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THE LONG-ACTING ANTICHOLINESTERASE DRUGS IN THE MANAGEMENT OF MYASTHENIA GRAVIS

HENRY ARANOW, JR., M.D., PAUL F. A. HOEFER, M.D., AND LEWIS P. ROWLAND, M.D.

NEW YORK, N. Y.

From the Departments of Medicine and Neurology, Columbia University College of Physicians and Surgeons, and the Medical Service and Neurological Institute of the Presbyterian Hospital, New York, N. Y.

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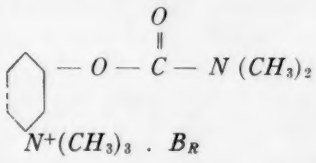
INTRODUCTION

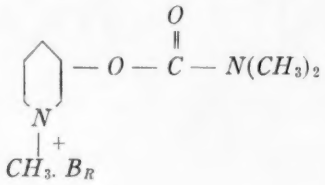
THE discovery of the striking action of physostigmine in myasthenia gravis by Walker, in 1934,[1] produced a change in the lives and prognosis of patients with this disease which has been compared with that change provided by the introduction of insulin in the lives of diabetic patients.

Loewi and Navratil[2] had shown that the major pharmacologic effects of physostigmine are due to its ability to inhibit cholinesterase (ChE), the enzyme which hydrolyzes acetylcholine. A host of compounds with significant anticholinesterase activity have been synthesized since 1930. In attempts to find more effective and or less toxic drugs for the myasthenic patient, a number of them have been given a therapeutic trial in this disease. The first of these was neostigmine, reported by Walker in 1935.[3] Its structural formula is:



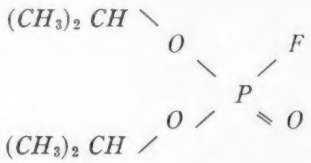
The OMPA used in this study was provided through the kindness of Dr. C. G. Weigand of Eli Lilly & Co.

Twenty-one years later oral neostigmine[4] continues to be the most widely used agent in the therapy of myasthenia gravis, although the recently introduced pyridostigmine is gaining in popularity. The structural formula of this drug is:



ALKYL PHOSPHATES

During the war years a group of alkyl phosphates which produced marked inhibition of ChE in serum, red blood cells, muscles, and brain was studied in connection with chemical warfare. Among these was diisopropyl fluorophosphate (DFP), the structural formula of which is:



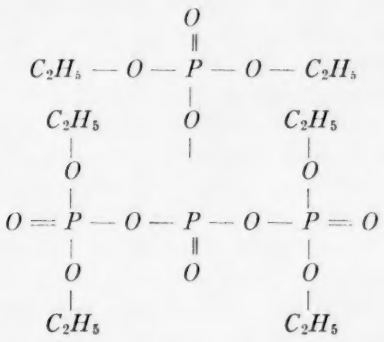
Less than one hour of contact between DFP and the cholinesterases of these various tissues produced an inhibition which could not be reversed by dilution or dialysis. This property led Gilman[5] to suggest that the action of DFP on patients with myasthenia gravis be studied. He and his colleagues administered the drug to 7 patients, and similar studies on myasthenic patients were reported from England[6] and Denmark.[7] A detailed report of the manifold actions of DFP in normal and myasthenic individuals was presented in a series of publications by Harvey, Grob, Lilienthal, and associates.[8-10]

In spite of the ability of DFP to produce irreversible inhibition of ChE, it has not proved a satisfactory agent for the management of patients with myasthenia gravis. Although intra-arterial injection of DFP into the affected extremity of a patient with myasthenia gravis resulted in a striking and protracted increase in strength and endurance in that extremity, toxic symptoms, particularly those related to the central nervous system, made it impossible to give systemic doses large enough to produce an effect as satisfactory as that usually obtained from neostigmine.

It was thought that the many undesirable central effects of DFP were related to its high lipoid solubility. Harvey and his co-workers[10] concluded: "The general treatment of myasthenia with anticholinesterase of this type must await the development of a substance which, by reason of its distribution within the body, will produce maximal effects in striated muscle before it destroys appreciable amounts of cholinesterase in the central nervous system."

Hexaethyltetraphosphate.—DuBois and Mangun[11] and Dayrit, Maury, and Seevers[12] examined some of the pharmacologic properties of hexaethyltetra-

phosphate (HETP) which had been introduced in Germany during World War II as an insecticide. Structural formula:

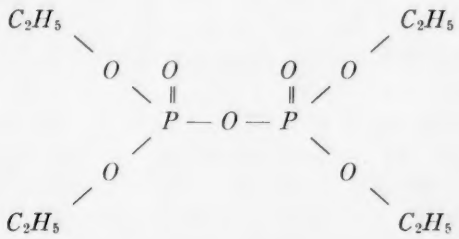


These workers found that HETP had a potent anticholinesterase action which was responsible for most of its effects. They also found a more rapid recovery of red blood cell and brain ChE activity in vivo than had been observed in animals in which a similar degree of inhibition had been produced by DFP. Brauer and Pessotti,[13] using isotopically tagged HETP, confirmed the observation that in vitro inhibition of the enzyme was irreversible.

Westerberg and Luros[14] administered HETP to three patients with myasthenia gravis in the fall of 1947. Central actions were prominent, and problems of dosage regulation were augmented by the marked instability of HETP in aqueous solution. Only parenteral therapy with HETP was attempted, and the authors felt that the drug could be safely administered only in the hospital.

Tetraethylpyrophosphate.—Burgen and his colleagues,[15,16] as well as Salerno and Coon[17] studied the pharmacologic actions of the closely allied tetraethylpyrophosphate (TEPP).

Structural formula:



They also compared its effects with those of HETP. Burgen and his associates gave it orally to 3 patients with myasthenia gravis. They showed it was possible to secure adequate control of myasthenic symptoms with orally administered TEPP and to substitute it for neostigmine in the management of patients. Although their data do not permit a comparison of the effects on maximally obtainable muscle strength produced by optimal dosage of each of the two medications, they suggest that this was no greater after treatment with TEPP than with neostigmine. The duration of the effects of TEPP, however, was much

greater. This resulted in a therapeutic effect which was less subject to fluctuation during the day and prevented the early morning weakness which is frequently experienced by patients taking neostigmine. Very few details are given in their paper about the period during which the final daily requirement of TEPP was determined, but they state, "Central side effects produced in all three patients during the process of dose stabilization, included vertigo, nystagmus, pallor, sweating, nausea, vomiting, and muscular twitching."

In 1949, Grob and Harvey[18] published an exhaustive and well-documented study of the actions of TEPP in man and of its use in the treatment of 12 patients with myasthenia gravis. They noted that TEPP was a more potent inhibitor of ChE derived from human plasma, red blood cells, muscle, and brain than were DFP and neostigmine. A shorter period of contact between enzyme and drug was needed by TEPP to produce "irreversible" inhibition than was required by DFP. After standing at body temperature for 20 hours, however, a much greater recovery of ChE activity was observed when the enzyme had been inhibited by TEPP than by DFP; in the latter instance there is practically no recovery of ChE activity. Koelle[19] had shown that reversible combination of ChE with neostigmine protected ChE, while it was bound to neostigmine, from irreversible inhibition by DFP. Grob and Harvey similarly found that ChE bound to neostigmine was protected from inactivation by TEPP. The increasing depression of ChE activity in plasma and red blood cells produced by graded or successive doses of TEPP was measured, as was the return of enzyme activity after the drug was withdrawn. The red cell ChE activity increased 10 per cent during the first 24 hours, and then about 2 per cent per day thereafter; this was approximately twice as rapid as the regeneration observed after inhibition by DFP. Although there were parallels between the depression of red cell ChE activity and the appearance of symptoms, no constant relationship between the presence or absence of symptoms and the precise degree of red cell ChE inhibition was observed. The activity of this enzyme could not be used as a guide in the regulation of dosage. The duration of the changes in muscle function caused by intra-arterially injected TEPP was markedly less than that occasioned by intra-arterial DFP, but more than twice that caused by intra-arterial neostigmine.

A remarkable depression of ChE activity is necessary before any clinical benefits become manifest in myasthenic patients. In the regulation of the patient this means that the initial, or "priming" dose is usually considerably greater than the maintenance dose. When the desired degree of esterase inhibition is attained, very small differences in the daily intake of TEPP produce marked alterations in the clinical well-being of the patient with myasthenia gravis. A few milligrams per day less than the optimal dosage may reduce muscle strength by as much as half; a few milligrams more than optimal dosage often result in an increase in muscle weakness, and distressing central side effects. When a maximal effect has been obtained from TEPP, neostigmine not infrequently diminishes rather than increases strength. Since repeated equal daily doses of TEPP may produce a slowly cumulative effect over a period of several weeks, very close observation is essential.

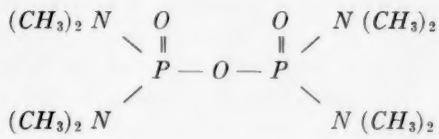
VOL
6
195

TEPP is readily hydrolyzed by water into inactive products, and its narrow therapeutic range is a major disadvantage when long-term oral administration is contemplated. Harvey and Grob indicated the hazards inherent in the use of an agent with these limitations in the management of patients with so variable a disease as myasthenia gravis, particularly when used outside of the hospital. In spite of its handicaps, 6 of their 12 patients shifted to TEPP preferred it because of the more predictable and constant control of myasthenic weakness throughout both day and night.

Similar conclusions were published by Stone and Rider[20] from their clinical experience with the use of TEPP in 8 myasthenic patients. They mentioned that the difference between ineffective underdosage and toxic overdosage might be as little as 0.5 mg. per day. In one of their patients the central effects of a small overdose produced a brief convulsive seizure.

Octamethyl Pyrophosphoramide.—In 1950, DuBois, Doull, and Coon[21-23] reported their studies on a new anticholinesterase drug which had predominantly peripheral actions. This was octamethyl pyrophosphoramide (OMPA), which was quite stable in aqueous solution.

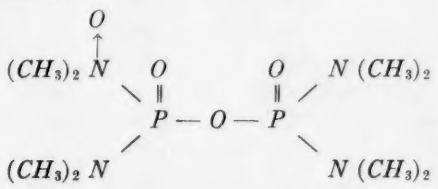
Structural formula:



Acute toxicity studies revealed that the LD_{50} was almost the same when the drug was given orally as when injected parenteraliy, indicating that OMPA was well absorbed from the gastrointestinal tract. Of great interest was the fact that the drug showed an essentially insignificant action against ChE in vitro, but was converted in vivo into a very potent inhibitor of this enzyme. Tissue slice experiments demonstrated that this conversion occurred in the liver. Independent studies by Gardiner and Kilby[24] in England yielded similar findings. It became apparent that the delay in the appearance of anti-ChE activity after the administration of OMPA could be ascribed to the time needed by the liver to perform this conversion.

The nature of the active metabolic conversion product has not been finally established in spite of considerable study.[25] Casida, Allen, and Stahmann[26] present data which lead them to conclude that this potent anti-ChE results from the oxidation of one, and only one, of the four nitrogen atoms in the OMPA molecule.

Structural formula (?):



From the therapeutic viewpoint the observation that even lethal doses of OMPA had essentially no effect on the ChE of the nervous system in vivo was of great importance. Acutely lethal doses which reduced the muscle ChE of poisoned animals to less than 7 per cent of control values caused negligible changes in brain ChE. This was confirmed by the absence of central nervous system effects, even in the agonal stages of poisoning. The absence of central nervous system actions is due to the inability of the active metabolite to cross the blood-brain barrier, since the active metabolite readily inhibits brain ChE in vitro.

The autonomic ("muscarinic") effects of OMPA and other anticholinesterases are readily blocked by atropine, which does not alter the actions at the neuromuscular junction.

Since OMPA seemed to possess the properties hoped for by Harvey and his associates[10] (vide supra), Rider and his colleagues employed it in the treatment of 6 patients with myasthenia gravis.[27]

In their initial trials, frequent determinations of serum and red blood cell ChE were made. During prolonged administration of OMPA very marked depression of the activities of these two enzymes was observed, but maintenance dosage could not be determined by estimation of either.

Four of their patients obtained a good therapeutic effect from neostigmine prior to their trial on OMPA. At the height of the neostigmine effect, physical examination showed only a slight degree of weakness, save for severe strabismus in one patient. These patients were successfully shifted from neostigmine to OMPA therapy. In one patient who continued to show incapacitating weakness on optimal neostigmine dosage, OMPA did not result in any increase in strength, although neostigmine requirements were notably lessened; this patient died while under therapy. In the sixth patient, the first whom they treated with OMPA, therapy was discontinued before optimal dosage was reached, because of epigastric pain.

CASE MATERIAL

Shortly after the appearance of the report by Rider and his co-workers,[27] we began our study of the effects of OMPA in patients with myasthenia gravis, and 21 patients with this disease have received this drug under our direction. Since experience had shown a lack of precise correlation between red cell and plasma ChE activity and optimal maintenance dosage, we decided to determine our dosage by clinical response only. When the patient's neostigmine requirements permitted it, OMPA was given at least 3 hours after and an hour before the administration of neostigmine. When uncomfortable muscarinic side effects occurred, they were usually controlled with atropine; some patients preferred the finer dosage adjustment permitted by tincture of belladonna. In a few patients in whom these side effects were particularly troublesome, trials were made of a number of synthetic autonomic blocking agents.

All patients were hospitalized during the initiation of therapy with OMPA, which was usually started with 7 or 8 mg. given orally at 12-hour intervals. The dose was measured in a tuberculin syringe and mixed with a small amount of

water in a medicine glass; the patient then rinsed the glass with another 30 to 60 ml. of water, and also drank this. In 3 patients, initial dosage was 5 mg. twice a day.

There were 15 women and 6 men in the group. The ages of the women ranged from 17 to 42 years, at the start of OMPA therapy, and averaged 27½ years; the ages of the men were between 26 and 61, and averaged 46 years.

GROUP I. PATIENTS WHO DID WELL ON OMPA THERAPY

Eight patients preferred therapy with OMPA to their previous regimens, and 4 of the 8 continue to be regulated on this medication. Two patients who preferred OMPA were shifted to pyridostigmine therapy because of decreasing supplies of OMPA; they had each been under OMPA treatment for 33 months and accepted the change with reluctance. The 4 patients who continue to take it have been managed on OMPA from 2½ to more than 4 years. Seven of these 8 had been managed on neostigmine from periods of 3 to 11 years before OMPA was started. One patient left the city after she had been well regulated on OMPA for 3 months; her supply of drug was exhausted at the end of a month, and she resumed taking neostigmine. The eighth patient was a 28-year-old woman with a complex and severe convulsive disorder of 23 years' duration, who had suffered from severe myasthenia gravis for 7 years. In spite of an intake of neostigmine bromide which ranged from 270 mg. to 360 mg. per day, she had great difficulty in chewing and swallowing. She was admitted to the hospital for a trial on some new anticonvulsant medications. After 6 weeks of treatment with varying combinations of these, OMPA treatment was begun. Neostigmine was gradually withdrawn, and she was discharged on 15 Mg. of OMPA twice a day; on this regimen her myasthenic symptoms were much better controlled than they had been on neostigmine. She continued to do well on this dosage for the next two weeks, but the management of her convulsive disorder was so difficult that it was thought unwise to attempt long-term therapy on still another experimental medication. OMPA dosage was progressively diminished and neostigmine resumed.

The clinical features shared by this group of patients who had the desired response to OMPA therapy merit examination.

All are women. Their ages at the onset of myasthenia gravis ranged from 14 to 28 years, averaging 21. Myasthenic symptoms are generalized in all. Some show more weakness in muscle innervated by the cranial nerves; in others the extremities are more severely affected. Prior to the exhibition of OMPA, neostigmine requirements ranged from 180 mg. (12 tablets) to 600 mg. (40 tablets) per day and averaged 375 mg. It is noteworthy that in all but one of these patients weakness was moderately, although far from ideally, controlled on optimal dosage of neostigmine. Frequent convulsive seizures were a major complication in the one exception.

At the time of discharge from the hospital, daily OMPA intake ranged from 12 to 30 mg. per day. In 4 patients maintenance dosage of OMPA was later reduced. The patient sent home on 30 mg. per day was readmitted 5 days later because of signs and symptoms of excessive inhibition of ChE. She was reregulated on 12 mg. per day, and was well controlled on approximately this dosage for the succeeding 3 years. A patient who was discharged on 24 mg. per day has had a thymectomy during the intervening years and is now very well controlled more than 4 years after the start of OMPA therapy on 11 mg. per day. The third patient gradually reduced her OMPA from 20 to 10 mg. per day, and the fourth has been able to lower the daily dosage from 25 mg. to 7 mg. per day over 3 years. The 12 mg. daily dosage of another has not needed change since discharge 27 months ago. In only one individual has it been necessary to increase the dosage, which was raised from 16 mg. to 29 mg. over a period of 6 months; she has been almost asymptomatic for 27 months on this latter dosage, but has symptoms if it is either increased or decreased.

GROUP II. PATIENT IN WHOM SIDE REACTIONS PREVENTED OMPA THERAPY

In only one patient did uncontrollable side actions make it impossible to continue with OMPA therapy.

VOL.
6
1957

This 34-year-old woman had suffered moderately severe myasthenia gravis for 18 years. During this period she had been an intelligent and cooperative subject for the trial of a number of neostigmine analogues. Her sister (included in Group I) developed myasthenia gravis about 12 years after the onset of the patient's disease and was successfully regulated on OMPA, which she is still taking.

Prior to the initiation of OMPA therapy, the patient was fairly well controlled by 375 mg. of neostigmine per day. Muscarinic side effects, mainly diarrhea, were inhibited by three tablets of amprotropine (50 mg.) each day.

OMPA dosage was gradually increased over 10 days, to 10 mg. every 12 hours. She felt stronger in the mornings than when taking neostigmine, but over-all strength did not seem greater, and diarrhea plagued her during the day and disturbed her sleep at night. Trials were made of a number of other cholinergic blocking agents, and the diarrhea was controlled, but a month later she complained of "some sort of block or congestion at the entrance of my stomach." Fluoroscopy demonstrated temporary stay of the barium in mid-esophagus, without evidence of spasm, which could be overcome by repeated swallowing movements.

Two weeks later she experienced excessive sweating and retrosternal discomfort while taking 11 mg. of OMPA every 12 hours, along with 750 mg. of diphenmethanil. With the sweating she felt weak and took 30 mg. of neostigmine bromide. This medication was followed by increased weakness, a sense of constriction in the throat accompanied by dyspnea and diarrhea. The symptoms of "cholinergic crisis" were fortunately recognized at a local hospital, and she improved markedly after the intravenous administration of 1.5 mg. of atropine sulfate. She omitted OMPA for the next few days and took only oral atropine and a few neostigmine tablets. OMPA was then resumed at a level of 7 mg. twice a day. Gradual increase to 9 mg. every 12 hours caused a recurrence of retrosternal discomfort and diarrhea. The patient was so impressed with her sister's favorable response to OMPA that she resisted suggestions that she discontinue OMPA. After discussion, she requested permission to increase atropine to tolerance, and during the next months raised her atropine sulfate intake to 15 mg. per day. This dosage eliminated the retrosternal pain, but did not adequately control the nocturnal diarrhea. Signs of atropinization were never observed, even on an intake of 1.2 mg. every 2 hours; unless she took it at 2-hour intervals during the night she was disturbed by cramps and diarrhea. This regimen offered no advantages over neostigmine and was abandoned. Two weeks later she was back on her pre-OMPA therapy, taking 360 mg. of neostigmine and 3.2 mg. of atropine sulfate each day.

GROUP III. PATIENTS WHO DIED AFTER DISCONTINUANCE OF OMPA

The 5 patients in this group died of myasthenia gravis from 3 weeks to 9 months after OMPA therapy had been discontinued. In 4 of these 5 patients, the severity of the myasthenia gravis rapidly increased; in the fifth the drug was prescribed in an attempt to make less onerous the life of a patient with extremely severe disease who had required medication at 2-hour intervals day and night for the preceding 7 years.

M. H., No. 07-59-36, a 17-year-old girl, suffered from a severe and steadily progressive myasthenia gravis of 22 months' duration. By February of 1952, she was unable to hold up her head, chew, or talk, and was choking on her saliva in spite of more than 400 mg. of neostigmine bromide each day. OMPA was administered, and she was sent home a month later, much stronger, taking 15 mg. twice a day. Although she was still stronger than on admission, increased weakness led to a decision to discontinue it and resume more flexible neostigmine management, and OMPA administration was finally terminated 7 weeks after she left the hospital. Six weeks after this, she was admitted to the hospital in respiratory failure, which was not materially improved by neostigmine in doses exceeding 500 mg. per day. She died in a respirator 26 days after admission.

M. B., No. 12-64-97, was 26 years old when she was admitted to the Neurological Institute complaining of deepening voice, dysphagia, and difficulty in pronouncing "k" sounds; these were of 2 months' duration. Symptoms were promptly, but briefly, abolished by a parenteral dose of neostigmine methyl sulfate. Five weeks after this diagnostic test, myasthenic symptoms had progressed to the point at which dyspnea was a real problem in spite of 30 mg. of neostigmine bromide every 2 hours day and night. OMPA was started in an attempt to diminish the need

for night medication and to permit the patient to get adequate sleep. The slow increase in OMPA dosage to 13 mg. *every 8 hours* did not permit reduction of neostigmine intake below 240 to 270 mg. per day. Nonmedical considerations led to her discharge on this regimen. Twenty-four hours after discharge she complained of gagging and nausea. This was shortly followed by cough, dysphagia, and aphonia. Parenteral neostigmine methyl sulfate, given at home, increased her dysphagia, and she experienced severe respiratory distress. An emergency tracheotomy was performed as soon as she arrived at the hospital, and she was placed in the respirator. All medications save atropine sulfate, antibiotics, and rectal Dilantin (for control of a long-standing convulsive disorder) were withdrawn, and the patient gradually improved, emerging from the respirator 12 days later. After 4 days during which relatively small doses of OMPA, along with oral neostigmine, were given, OMPA was permanently discontinued; it was felt that the hazard of another "cholinergic crisis" in this extremely severe case of myasthenia precluded its use. The patient's disease remained maximally severe in spite of a thymectomy performed 3½ months after readmission. Four and one-half months after thymectomy she was transferred to another hospital and died there a month later.

H. W., No. 11-67-07, a 61-year-old shoe salesman with myasthenia gravis of 8 months' duration, was given OMPA when increasing doses of neostigmine failed to relieve weakness. Although OMPA was progressively increased to 20 mg. every 12 hours, he required 540 mg. of neostigmine in addition to control increasing dysphagia and respiratory difficulty. Since the rapid advance of the disease appeared to make respirator care inevitable, OMPA dosage was sharply reduced with a view to withdrawing it completely; parenteral neostigmine was increased as OMPA intake fell. Four days later respiratory collapse made tracheotomy and mechanical respiratory therapy mandatory, and OMPA was discontinued and never again administered. After a week in the respirator the patient was able to get along without mechanical aid to respiration while taking neostigmine methyl sulfate 1.5 mg. intramuscularly every 1½ hours. For the next 11 days he did fairly well, although his dysphagia prevented the use of oral medication. There was then a sharp deterioration in his condition, and he died shortly after being put back in the respirator. Post-mortem examination showed an old myocardial infarction which had been diagnosed six years before the onset of myasthenia gravis. There was no recent infarction, but scattered through the myocardium were many areas of frank necrosis of myocardial fibers, and of myocardial degeneration.[33]

R. T., No. 02-16-53, aged 33 years, an Italian-born mechanic, was admitted 6 weeks after the onset of myasthenia gravis with weakness of the muscles innervated by the cranial nerves. He concealed a history of convulsive seizures and psychiatric difficulties which was obtained from other informants shortly before his death. He was discharged on 5 mg. of OMPA 4 times a day, supplemented by 15 mg. of neostigmine bromide before each meal. He did fairly well on this regimen for 2 months. He was then admitted shortly after an early morning convulsive seizure which was described as tonic and clonic and was followed by a period of flaccid weakness. OMPA was discontinued, and he was reregulated on 30 mg. of neostigmine bromide every 2 hours supplemented by ephedrine and atropine. An electroencephalogram during this admission was normal. Increasing weakness necessitated increasing his neostigmine to 30 mg. every 1½ hours. Five weeks after the convulsion he was readmitted because of a respiratory infection. Antibiotics were given, and his neostigmine further increased. Eighteen hours before his death he had a grand mal seizure, following which he became apneic and cyanotic. An emergency tracheotomy was performed, Dilantin sodium was given by rectum, and he was placed in the respirator. In spite of further Dilantin and heavy sedation, two protracted, generalized convulsions occurred in the respirator, and he died in shock with a temperature of 105.8° F. Blood and spinal fluid cultures were sterile, and permission for autopsy was refused.

M. G., No. 82-50-97, was a 35-year-old graduate nurse who had been disabled by maximally severe myasthenia gravis for more than 7 years. Shortly after the onset of her illness, at a time when she needed about 225 mg. of neostigmine to control her symptoms, a large thymoma was removed. Her postoperative course was smooth, and she left the hospital with her myasthenic symptoms controlled by about one-third of her preoperative dosage of neostigmine. Three weeks later there was a sudden worsening of her disease, and her dosage requirements rose to 45 mg. of

neostigmine every 2 hours day and night. Muscarinic side effects necessitated 0.6 mg. of atropine sulfate with each dose of neostigmine. Even on this dosage she was rarely able to walk unaided, experienced great difficulty in chewing and swallowing, and was unable to sit without support. On two occasions prior to her trial on OMPA, respiratory crises requiring tracheotomy and varying periods of respirator care had occurred. The hazards of a long-acting anticholinesterase drug in a patient with disease as severe as hers were fully discussed, but she requested a trial because she found her life almost insupportable on the regimen described above; she said she would be gratified if no more was accomplished than to eliminate the need of being awakened every 2 hours during the night for medication.

OMPA was started in dosage of 5 mg. every 8 hours. Although the dosage of OMPA was gradually increased to 13 mg. every 8 hours she did not find it possible to decrease her neostigmine below her usual 540 mg. per day, and she continued to take 0.6 mg. of atropine sulfate every 2 hours. When no improvement was evident after 2½ weeks of therapy, the risks were again reviewed with her, but she expressed a firm desire to continue. Three days later she had an episode of respiratory distress requiring intratracheal intubation and 8 hours in the mechanical respirator; this mishap was apparently the result of excessive salivation, and she improved after parenteral atropine administration. OMPA was discontinued and was not given again during the remaining 9 months of her life. The day after her stay in the respirator she noted no increase in weakness although she received neither OMPA nor neostigmine, suggesting that the episode of the preceding day may have represented the result of overtreatment as well as inadequate control of muscarinic side effects. Increasing dysphagia the following day made parenteral therapy mandatory, and she was given 1.5 mg. of neostigmine methyl sulfate along with 1 mg. of atropine intramuscularly every 2 hours. That night, 42 hours after OMPA was withdrawn, she had abdominal pain and nausea. After an uneventful night, severe abdominal pain recurred the next day, and 10 minutes later she became apneic, unconscious, and covered with a cold sweat. Artificial respiration and intratracheal intubation were followed by tracheotomy and mechanical respirator care. The abdominal pain was still present when she recovered consciousness a few minutes later, and was accompanied by a leukocytosis of 17,300 with 92 per cent polymorphonuclears. Pain and leukocytosis cleared after 24 hours and were never explained. She remained in the respirator for 10 days, and in the hospital for several months. Dysphagia continued to be so severe that high caloric feedings were given for many weeks through a plastic nasal catheter. She was finally discharged on the same regimen which she had been following at the time of admission, and died suddenly at home 5 months later, 8½ years after the onset of her illness.

GROUP IV. PATIENTS WHO DIED WHILE RECEIVING OMPA THERAPY

This group comprises 7 patients who died while receiving OMPA. Of these, 3 were never well controlled even on large doses of OMPA supplemented with neostigmine. In 2 of these 3, death followed sharp reductions in OMPA dosage made after the patients had been discharged to other hospitals. Respiratory crises had occurred in these 2 patients while final OMPA dosage was being determined under our care, and they were transferred when it became apparent that very prolonged hospital care would be required.

C. C., No. 10-68-80, a 47-year-old Chinese man, was admitted to the hospital 5 months after the onset of myasthenia gravis. Increasing doses of neostigmine afforded only fair control of weakness, and a 10-day course of cortisone was given without improvement. OMPA therapy was begun 3 weeks later, but it was not possible to reduce the patient's neostigmine intake below 37.5 mg. every 2 hours day and night, even after 2 weeks of treatment. At the end of 4 weeks he was taking 15 mg. of OMPA every 12 hours, and neostigmine requirements had fallen to 180 mg. per day, but generalized weakness continued to be severe. Five weeks after initiation of OMPA he complained of respiratory difficulty and neostigmine dosage was slightly increased. That night he was placed in the mechanical respirator before either intratracheal intubation or tracheotomy had been performed. Severe hypoxia required emergency tracheotomy in the respirator, and all anti-ChE medication was suspended. Respiratory therapy was required for 9 days before the patient could again breathe unassisted. OMPA was started again. A month later optimal strength was achieved on a dosage of 15 mg. every 12 hours, but he was still disabled by generalized weak-

ness and difficulty in chewing. Discharge to his home was out of the question, and changes in the regimen produced no increase in strength, so that, at the end of 6 months, he was transferred to another hospital for long-term care. He died there 5 weeks later.

S. B., No. 17-76-83, a 24-year-old housewife, was transferred to the Neurological Institute from another hospital for myasthenia gravis of increasing severity of 15 months' duration. Her disease began during the early part of her second pregnancy and required hospitalization 3 months after a normal delivery. She had experienced frequent generalized convulsions from the second to the seventh month of her first pregnancy 4 years before, but these had cleared completely and had not recurred. Three months of neostigmine therapy in another hospital failed to control her symptoms and transfer by ambulance was arranged. Respiratory failure occurred suddenly 2 days after admission, and tracheotomy and respirator treatment were required. Save for a 2-day period in January of 1955, the tracheotomy tube remained in place until her discharge to another hospital almost 15 months later.

During the succeeding 10 months she was in and out of the respirator on a variety of regimens based on neostigmine and pyridostigmine. A 10-day course of ACTH therapy was given 5 months after admission, without apparent effect. Respirator care was continuously required from the latter part of her ninth hospital month until after OMPA therapy was started during her twelfth hospital month. A single convulsion occurred 10 months after admission, and Dilantin was administered for the remainder of her hospital stay without recurrence of seizures.

OL.
6
957

The decision to employ OMPA was taken after full review of its hazards. Improvement was dramatic. OMPA was started in dosage of 7 mg. twice a day, given along with 0.6 mg. atropine sulfate, and was very gradually increased. On the twenty-fifth day she was able to leave the respirator, and her regimen was stabilized when she was taking 9 mg. of OMPA every 12 hours, and a total of 9 mg. of atropine sulfate during each day. Progress was slow and continuous, and she walked again for the first time in 14 months. Three days later she was able to swallow liquids for the first time in 10 months, and the nasogastric tube which had been required for the preceding 11 months was removed. In order that she might be near her family, transfer to a hospital in South Carolina was arranged by special airplane. There it was decided to withdraw OMPA gradually and to reregulate her on neostigmine which had failed repeatedly during the preceding 17 months. By the time of her death 7 weeks later, OMPA dosage had been reduced to 5 mg. every 12 hours, supplemented by 45 mg. of neostigmine every 3 hours, day and night. Several episodes of respiratory failure occurred, and autopsy revealed complete atelectasis of both lower lobes and considerable atelectasis in the remaining 3 lobes. The bronchi contained large amounts of thick, stringy mucoid material. There was no thymoma.

G. P., No. 96-55-42, a 42-year-old housewife, noted the onset of myasthenia gravis in September, 1949. Initially myasthenic symptoms were mild and responded to relatively small amounts of neostigmine, but by June of 1950, she was taking 195 mg. per day and having trouble in swallowing her medication in the morning. In spite of an increase in her neostigmine to 555 mg. per day in the succeeding 9 months, there was little improvement, and by August of 1951, she said that she feared to go to sleep because of frequent respiratory weakness. Dysphagia resulted in a loss of 25 pounds in weight and the need for many parenteral neostigmine injections.

OMPA was started in February, 1952, and at the end of 10 days her neostigmine dosage was halved to 270 mg.; she was discharged taking 12.5 mg. of OMPA every 12 hours. Shortly thereafter she eliminated one dose of OMPA, since she either could not or was unwilling to reduce her neostigmine intake below 2 tablets (30 mg.) every 2 hours day and night. On this regimen she felt definitely stronger than prior to the institution of OMPA but 3 months later complained that weakness was again increasing. An additional 5 mg. of OMPA was taken in the morning, but pharyngeal and bronchial secretions became troublesome, and dysphagia finally became severe enough to require admission 10 months after the start of OMPA therapy. She was considerably benefited by rehydration and pharyngeal suction, but her inability to swallow required elective tracheotomy a week later. Respiratory muscular strength seemed adequate, and mechanical aid to respiration was not required. During the week preceding tracheotomy, OMPA had been gradually increased to 12.5 mg. every 12 hours in addition to 30 mg. of neostigmine bromide every 2 hours. Atropine sulfate 0.6 mg. was given with every second dose of neostigmine.

Evidence of patchy pneumonitis and atelectasis was noted on the day after tracheotomy, and antibiotic therapy was begun. Respirations seemed adequate, and the respirator in her room was not used.

Two days later she was found dead in bed 5 minutes after an examination by the nurse had revealed no apparent change in her condition.

Post-mortem examination revealed lobular pneumonia in the right lung and a thymoma which measured 5 x 1.5 x 1.5 cm.

M. A., No. 95-75-12, a 24-year-old plumber's helper, was admitted to the Neurological Institute in June, 1949, for myasthenia gravis of 11 months' duration. Neostigmine sulfate 330 mg. afforded enough strength to permit him to continue with his work, although he had to be awakened to take medication at 4. A.M. each day in order to be able to swallow his pills on arising. Exacerbations of disease followed rather frequent upper respiratory infections.

He was admitted for OMPA therapy in May, 1952; at this time his neostigmine requirement varied from 420 to 450 mg. per day. He was discharged 2 weeks later taking 10 mg. of OMPA every 12 hours, supplemented by 15 mg. of neostigmine 4 time a day.

Over the succeeding months his strength improved, he reduced the dosage of OMPA to 7 mg. every 12 hours, and he took only 3 tablets of neostigmine per day. He had become a master plumber and was working a full 40-hour week.

This state of well-being continued until June, 1953, when a respiratory infection led to increasing dyspnea, in spite of an augmentation of neostigmine to 300 mg. per day and 3 parenteral injections of neostigmine methyl sulfate 1 mg. Chest x-ray was clear. Intravenous injection of 10 mg. of edrophonium chloride (Tensilon) produced no significant changes. He reduced his OMPA to 6 mg. twice a day supplemented by 150 mg. of neostigmine.

Two weeks later he was readmitted with a right middle lobe pneumonia, and a "Tensilon test"[34] suggested that dosage of anticholinesterase medications was optimal. Antibiotics were started, and the "Coflator" was able to clear the bronchi which his ineffective cough had permitted to become obstructed. OMPA was withdrawn, and an elective tracheotomy was performed before he was placed in the mechanical respirator. Neostigmine was given parenterally and he was able to leave the respirator after 16 hours. When he had been stabilized on oral neostigmine he requested that OMPA be given again, and the latter was readministered 9 days after it had been withdrawn.

Following this pneumonia he never again regained his earlier strength and was unable to resume his work as a plumber. The regimen which produced maximal strength included 9 mg. of OMPA twice a day supplemented by 90 to 105 mg. of neostigmine. On this regimen he could do little more than sit around the house.

Ten months after his initial bout of pneumonia he was admitted to a suburban hospital with another attack of pneumonia; he died there in respiratory failure shortly after admission.

Three patients died very suddenly. Their symptoms of myasthenia gravis seemed well controlled until less than a few hours before exitus.

M. A. E., No. 09-53-80, an 18-year-old girl, was admitted to the Neurological Institute in May, 1952. She had been quite well until 2 months before when an occasional nasality of her voice was noted. In the 4 weeks prior to admission, ptosis, difficulty in chewing, regurgitation of fluids through her nose, and dysarthria became manifest. There was no roentgenographic evidence of thymoma.

An injection of 1.5 mg. of neostigmine methyl sulfate produced striking improvement, and she was discharged after 9 days, taking 30 mg. of neostigmine bromide 5 times a day. In spite of a steadily increasing dosage of neostigmine, symptoms and signs became increasingly severe. By Sept. 14, 1952, she was severely incapacitated although her daily neostigmine intake was 525 mg. Attempts to increase her strength by altering her neostigmine regimen were unsuccessful, and OMPA was started 2 weeks later. An initial 5 mg. dose was given parenterally, and was followed in 15 minutes by an enormous increase in bronchial and pharyngeal secretions which required tracheotomy followed by respirator care. She required continuous respirator therapy for 5 days and was able to discontinue it completely after 12 days.

Three days afterward OMPA was administered orally in dosage of 5 mg. twice a day. Severe dysphagia made it necessary to continue the tracheotomy for another 2 weeks. OMPA was

VOL 6 195

slowly increased to 10 mg. twice a day, and muscarinic side effects were controlled by 1.8 mg. of atropine each day. She took 30 mg. of neostigmine shortly before lunch and dinner. When discharged in November, 1952, she was still troubled by dysphagia, her voice was weak, and there was considerable facial muscle weakness.

When seen in the outpatient department 2 weeks later she reported improvement in phonation and swallowing but said that the neostigmine produced cramps in spite of 0.3 mg. of atropine sulfate. OMPA was increased to 12 mg. every 12 hours, and neostigmine was reduced to 15 mg. twice a day.

Four weeks after discharge chewing and swallowing continued to improve, but she felt that her arms, voice, neck, and legs were weaker. Neostigmine still produced cramps. No change was made in the anticholinesterase medications.

The 3 days after her last clinic visit were marked by surprisingly good muscular strength. She was able to manage a full day of Christmas shopping without significant symptoms. At bedtime she had some vague malaise and slight dyspnea, although less than she had frequently experienced previously. She requested an injection of neostigmine; this was given, although the parents were unable to detect any objective change. At the patient's request an ambulance was summoned. Neither the parents nor the ambulance attendants noted any evidence of respiratory distress, but the patient suddenly died in the ambulance less than two hours after her first complaint of mild malaise.

During the 3 days preceding her death she had experienced no nausea, vomiting, diarrhea, or cramps. Fasciculations had not been noted. Atropine sulfate intake had ranged from only 2.1 to 2.4 mg. per day.

Complete autopsy revealed no abnormality save for a diffusely hyperplastic thymus which weighed 34 Gm. and a few perivascular lymphocytic infiltrations in the muscles.

J. A., No. 09-02-99, a 50-year-old bank messenger, was well until July, 1951, when right ptosis became manifest. This was shortly followed by generalized weakness. The diagnosis of myasthenia gravis was made 2 months after the onset of symptoms, and neostigmine therapy was started at another hospital. During the succeeding 8 months his disease became much more severe, and neostigmine requirements increased greatly. Ten months after his illness began the patient experienced occasional dyspnea in spite of 360 mg. of neostigmine each day. He was admitted to the Neurological Institute for OMPA treatment. Two weeks later he was discharged taking 15 mg. of OMPA every 12 hours and 30 mg. of neostigmine every 4 hours; four doses of atropine sulfate, 0.6 mg., were required each day to control muscarinic side effects. On this regimen he reported increased strength.

At his OPD visit 2 weeks after discharge he reported that he no longer needed medication during the night, and weakness was less; he was troubled by diarrhea after the morning dose of OMPA but had had only one brief bout of dyspnea after leaving the hospital. Neostigmine dosage was reduced to 22.5 mg. every 4 hours during the day, and the regimen was not otherwise changed.

Two days later a sudden bout of diarrhea led to a reduction in OMPA dosage to 13 mg. twice a day. Four days after his clinic visit, after an asymptomatic day, he noted the onset of dyspnea and died at home within half an hour before medical attention could be obtained.

C. S., No. 04-06-09, a 57-year-old electrician, was admitted in April, 1951, because of difficulty which he had had in speaking and swallowing for 7 weeks. Seven and one-half years earlier he had experienced intermittent diplopia during a 6-month period. This had disappeared after a cholecystectomy, and he was symptom free for 3 years. On rare occasions during the succeeding 4¼ years he noted occasional and not very troublesome diplopia, but he did not seek medical aid until the appearance of dysarthria and dysphagia. Symptoms and signs responded dramatically to neostigmine, and he was able to return to a very arduous job, taking 15 mg. of neostigmine bromide 6 times a day.

During the next 4 months he not infrequently worked more than one shift in 24 hours; the plant was so large that he bicycled from one part to another. He needed increasing amounts of neostigmine, and requirements in September were 4 times those of April.

His disease and need for medication remained stable for the next 6 months, but there was then a striking increase in weakness which was not adequately controlled by raising neostigmine dosage to 540 mg. per day.

Fifteen months after the initiation of neostigmine therapy, the patient requested admission for a trial on OMPA. In spite of amounts of OMPA which were increased to 18 mg. every 12 hours, supplemented by neostigmine bromide, 30 mg. every 4 hours, there was no material gain in strength. Although the regimen was not further altered, he reported a diminution in his symptoms and was discharged.

During the next 11 days at home he felt that he was about the same as he had been before starting OMPA. An attempt to return to work was followed by a striking increase in weakness, dysphagia, chewing difficulty, and ptosis. He continued to take 18 mg. of OMPA morning and evening but decided to shorten the interval between his 30 mg. doses of neostigmine to 3 hours; he took 0.4 mg. of atropine sulfate with each dose of neostigmine. Some doses of neostigmine were followed by brief fasciculations in his calves. The increased neostigmine intake led to severe diarrhea during the succeeding week, so he decreased his OMPA to 12 mg. every 12 hours but shortened the interval between his 30 mg. neostigmine doses to 2 hours.

Although he had no change in symptomatology, he was advised by telephone to come to the hospital.

During the drive to the hospital he suddenly complained of increase in weakness. By the time he reached the ward he was gasping. Parenteral neostigmine produced no improvement, and he lost consciousness a few minutes later. Immediate tracheotomy and respirator therapy did not restore consciousness, and he died in the respirator 48 hours later.

No thymic tissue was found at autopsy. There were bilateral pleural effusions and a nonconfluent lobular pneumonia superimposed on severe pulmonary edema.

DISCUSSION

In 1952, Gregory, Futch, and Stone[28] reported on their results with OMPA in the management of 16 patients with myasthenia gravis. At the time they submitted their report, their patients had been treated from 2 to 20 months, with a mean duration of therapy of 10 months. They stated that *all* of their patients found OMPA to be the best agent with which they had been treated. In their experience abdominal cramps and diarrhea were the earliest toxic symptoms and were controlled in all but one patient by adequate doses of belladonna. The undesirable side effects of neostigmine were noted to be greatly increased in patients taking maintenance doses of OMPA. Four of their 16 patients died during the period of study. Details are given about only one of the four deaths, which occurred in a patient with concomitant and severe liver disease. The other three deaths occurred outside of the hospital and were sudden. They were said to be due to respiratory weakness unresponsive to neostigmine, but no mention is made of the presence or absence of fasciculations, muscarinic side effects, or of coincident respiratory infection. The relevance of these latter manifestations was emphasized by Wilson, Williams, and Miller[29] in a case report noting that overdosage of OMPA had the same lethal potentialities that had been found by Grob and Harvey[18] in their study of TEPP. There is a striking similarity between the patient poisoned by TEPP and the patient poisoned by OMPA. In the latter, overdosage had not been sufficient to cause respiratory arrest, and atropine alone sufficed to produce striking improvement. The analogous aspects of myasthenic and "cholinergic" crises were indicated, and the need for awareness of these by all concerned in the management of the myasthenic patient was underlined.

In 1953, Schulman, Rider, and Richter,[30] who participated in the first study of the use of OMPA in myasthenia gravis,[27] published the results of a longer

study which included 15 patients. Seven of these died during the period covered by the report, and it was their opinion that death in 3 was attributable directly to intoxication by the drug. These 3 cases bore a striking resemblance to the three reported by Gregory, Futch, and Stone[28] in which death occurred suddenly, and to the last 3 cases in our series. Osserman and Kaplan[31] reported on 12 patients treated with OMPA and ascribed two of the five deaths in their series to cholinergic crises; no details are given.

Sudden death is a well-known feature of myasthenia gravis, and it is far from clear that the nine instances of sudden exitus in the combined series of Schulman, Rider, and Richter,[30] Gregory, Futch, and Stone,[28] and ourselves can be ascribed to an excessive inhibition of ChE by the therapeutic agents used. In his recent review of myasthenia crises, Tether[32] described 16 fatal cases in half of which death occurred suddenly. None of these was during therapy with a long-acting anticholinesterase agent. In our recent study of fatalities in myasthenia gravis,[33] 13 of the 39 deaths were sudden, and only 3 of these patients were taking a long-acting anticholinesterase drug.

VOL.
6
1957

On the other hand, in Tether's series of 186 severe or moderately severe myasthenics there were only 8 instances of sudden death in 12 years. In the group of 53 patients treated with OMPA there were 9 instances of sudden death in two years. Although there was undoubtedly a higher proportion of severely ill patients among those on OMPA therapy, the difference in incidence of this type of exitus is striking.

Among the usual evidences of overdosage with anti-ChE agents is the appearance of "nicotinic" signs, even if the "muscarinic" side actions are blocked by atropine. None of the patients in our series who died suddenly was taking more than 2.5 mg. of atropine sulfate per day; many patients managed on neostigmine habitually use much more. Fasciculation is usually prominent among nicotinic side actions. It was noted by DuBois, Doull, and Coon[23] in their pharmacologic studies and was a striking feature of the instances of TEPP overdosage described by Grob and Harvey.[18] It is an important sign of supraoptimal anti-ChE dosage in the "Tensilon test" described by Osserman, Kaplan, and Besson.[34] Rowland and his associates,[35] however, did not constantly find it at the time of weakness induced by excessive doses of neostigmine, but there is some evidence to suggest that neostigmine has important actions at the neuromuscular junction in addition to its anti-ChE action.[36-40] In only one (C.S.) of our patients who died while taking OMPA was fasciculation noted, and it was not mentioned in the description of the only one of the patients of Schulman, Rider, and Richter[30] who was under observation at the time of fatal crisis.

In appraising the hazards of therapy with long-acting anti-ChE drugs, over-all mortality figures have little meaning. A large proportion of the patients in each of the published series was comprised of cases of progressive myasthenia gravis who were responding poorly to other drugs. Against these hazards must be weighed the significant number of patients with myasthenia gravis who have been given a thorough trial on other drugs and who are better regulated and are able to lead happier and more useful lives when taking OMPA than when maintained on the short-acting anti-ChE drugs.

Grob and Harvey[41] reviewed the features of poisoning produced by a variety of long-acting anti-ChE agents—"nerve gases," insecticides, and drugs. The great value of adequate quantities of atropine administered early, and of artificial respiration, in the therapy of such poisoning was stressed.

A recent development of great potential importance in this field has been the discovery by Wilson and his colleagues[42,43] that ChE which has been inhibited "irreversibly" by alkylphosphates can be reactivated by certain "nucleophilic agents" such as picolinhydroxamic acid. With them the effects of uniformly lethal doses of alkylphosphates have been reversed in animals.[44] Although the agents studied so far do not reverse the inhibition of ChE produced by the active metabolite derived from OMPA, this line of research offers promise. A great deal remains to be done, however, before these elegant pharmacologic experiments can have direct therapeutic relevance to the problem of OMPA overdosage in the day-to-day management of myasthenia gravis.

The published series and our own material have been studied with a view to determining the characteristic clinical features of patients who do well on OMPA and of those to whom its administration appears to be hazardous.

The characteristics of the group of patients responding well are quite definite. Although neostigmine requirements prior to the start of treatment with OMPA varied widely—from 180 mg. to 600 mg. per day—all were reasonably well controlled on optimal doses of neostigmine, and none was the victim of progressive disease. OMPA enabled them greatly to enlarge their sphere of activities and productive work because it gave more constant and predictable relief of easy fatigability and weakness. None requires more than 30 mg. per day.

It will be noted that our group of 6 patients who preferred and were benefited by OMPA over a period of several years very closely resembles the group of 6 reported by Schulman, Rider, and Richter[30] who found OMPA more satisfactory than neostigmine. The almost uniformly unsatisfactory experience with OMPA reported by Osserman, Kaplan, and Besson[34] has not been shared by other workers, but the daily doses used by them were so different from those administered by the others that the discordant results do not seem surprising.

In patients whose weakness has not been reasonably well controlled by neostigmine, and in patients with myasthenia which is progressing in severity, the use of OMPA serves no useful purpose. Six of the 7 deaths in the series of Schulman, Rider, and Richter[30] occurred in patients with severe or progressive disease, and the seventh occurred in a patient who did not return for observation and altered his OMPA dosage on his own initiative. Ten of the 12 patients in our series who died during the period of study received OMPA because other medications had failed to halt their increasing weakness. The use of long-acting anticholinesterase medications in the management of patients with stable but extremely severe myasthenia is hazardous and should be undertaken with full awareness of the nature of its dangers.

SUMMARY

1. The published studies on the treatment of myasthenia gravis with long-acting anticholinesterase drugs—di-isopropylfluorophosphate (DFP), hexaethyltetraphosphate (HETP), tetraethylpyrophosphate (TEPP), and octamethyl

pyrophosphoramide (OMPA)—have been reviewed and correlated with studies on 21 patients treated by us with OMPA.

2. The data indicate that OMPA possesses most of the desirable qualities which could be expected of long-acting anticholinesterase compound for the use in the management of myasthenia gravis: it is stable in aqueous solution; it is well absorbed when administered orally; it is highly effective in producing "irreversible" inhibition of ChE; finally, it is essentially free of actions on the central nervous system.

The data also suggest that it is improbable that any other compound whose effects are due to more or less "irreversible" inhibition of ChE will prove significantly superior to OMPA in the management of patients with myasthenia gravis.

3. Long-acting anti-ChE agents should not be administered to patients with myasthenia gravis of progressively increasing severity and should be given only with great caution to patients with stable but severe disease.

4. Octamethyl pyrophosphoramide (OMPA) is an excellent agent for the treatment of the patient with only moderately severe and stable myasthenia gravis. By its use some patients can be transformed from semi-invalidism to essentially normal activity.

5. Experience with the long-acting anticholinesterase drugs demonstrates that even maximal inhibition of peripheral ChE may fail to control myasthenic weakness. Adequate management of severe or progressive instances of the disease must await a better understanding of its pathologic physiology.

VOL.
6
1957

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VOL
6
195

CLINICAL MANIFESTATIONS OF HISTIOCYTOSIS X IN THE ADULT

JOHN L. DADEY, M.D., AND LEWIS M. HURXTHAL, M.D.

BOSTON, MASS.

From the Department of Internal Medicine, The Lahey Clinic, Boston, Mass.

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OL.
6
957

AS a result of the case reports of histiocytosis X or normocholesteremic xanthomatosis published during the past three decades,[1-9] it has been possible to appreciate the protean manifestations of this group of diseases. It is now apparent that these manifestations encompass many clinical fields and that the disease may be encountered in various specialties.

The purpose of this paper is to call attention to the varying clinical features of the disease and to analyze the experiences at the Lahey Clinic in this regard.

CLASSIFICATION

Because of the manner in which they have evolved, the nosologic classification and nomenclature of this group of diseases have been confusing. The three syndromes of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease, which were originally regarded as distinct entities, are now considered to be interrelated manifestations of a single malady.[10] The term histiocytosis X has been suggested by Lichtenstein[11] to include these three diseases all of which are characterized pathologically by a histiocytic proliferation of unknown etiology. Thannhauser[12] has used the terms "essential xanthomatosis of the normocholesteremic type" and "eosinophilic xanthomatous granuloma" as synonyms of histiocytosis X.

Eosinophilic granuloma has been a relatively benign disorder with single or multiple skeletal lesions histologically consisting primarily of a proliferation of histiocytes and eosinophils. The Hand-Schüller-Christian syndrome is classically characterized by multiple round defects in the skull, unilateral or bilateral exophthalmos, and diabetes insipidus. It is not necessary, however, that all three of these abnormalities exist and other manifestations in combination with one or two of these are just as typical of the syndrome that, in common usage, goes by the name of Hand-Schüller-Christian disease. A histiocytic granuloma with histiocytic infiltration by cholesterol, resulting in the so-called foam cells, constitutes the pathologic lesion. Invasion of eosinophilic cells is also characteristic of the lesion, particularly in the early development of the disease. This chronic disorder usually occurs in children but may be found in young adults and rarely in older individuals. The Letterer-Siwe syndrome

is characterized by the development of multiple areas of proliferating histiocytes which are usually devoid of cholesterol esters in the visceral organs. This form of the disease, which occurs almost exclusively in children, particularly under the age of three years, represents the acute entity and is clinically associated with more acute clinical manifestations than are the other two syndromes.

ORGAN INVOLVEMENT

In general, the organs or systems chiefly involved in histiocytosis X are bones, brain, lungs, skin, reticuloendothelial system, and mucous membranes (oral, anal, and genital).

The clinical picture in any individual patient is significantly influenced by such factors as (a) dispersion of lesions (localized or disseminated), (b) severity of the disease, which may possibly be related to host susceptibility, (c) age of the patient, with certain reservations, and (d) extensive involvement of crucial organs, particularly the lungs and pituitary body.[11]

Since solitary eosinophilic granuloma of bone may involve the skull, ribs, femur, vertebrae, pelvis, mandible, humerus, and clavicle most commonly, local pain or swelling in any of these sites may represent the initial and often only clinical manifestation. Clinically, eosinophilic granuloma of bone may be a completely silent lesion, and often symptoms are first noticed after a bone injury. Spontaneous fractures may occur. If lesions in the bones are located near the joints, they may penetrate into the joints and involve them. Because the skull roentgenograms of bony defects have the appearance of a geographic map, these skulls are accordingly designated as "geographic map skulls."

The bones of the orbit and sella turcica seem to be sites of predilection, and this accounts for the frequency of exophthalmos and diabetes insipidus. The characteristic diabetes insipidus is often caused by invasion of the pituitary from the sella turcica. Lesions of the sella, however, may occur without invasion of the pituitary and without the existence of diabetes insipidus.

Most of the intracranial symptoms are produced by dural and epidural masses of the xanthomatous material. Hence, convulsions, cerebellar symptoms, and other neurologic manifestations of intracranial involvement may result. Lesions of eosinophilic xanthomatous granulomas of the dura and brain involving the pituitary, stalk, and most frequently the tuber cinereum and hypothalamic region result in diabetes insipidus. Other endocrinologic disturbances such as retardation of growth may result from pituitary involvement.

Since the proliferative xanthoma-like masses originating in neighboring bony structures may involve the middle ear cavity, external auditory canal, and antrum, clinical manifestations in these regions may result. In the middle ear or external auditory canal the masses may easily be mistaken for aural polyps or cholesteatomas,[13] whereas in the orbit or antrum they may simulate tumors.

Otologic symptomatology, therefore, includes manifestations due to otitis media, mastoiditis, labyrinthitis, seventh and eighth cranial nerve involvement, otitis externa, and sinusitis.[14,15] Thus, impairment of hearing, a chronic ear discharge, and vertigo may constitute presenting symptoms.

Oral lesions which have been described are necrotizing gingivitis and large cystlike lesions in the mandible causing displacement, loosening, and finally extrusion of the teeth.[16] These lesions contain the characteristic granulation tissue and fat storage cells.

Xanthoma disseminatum of the skin[17] may occur in eosinophilic xanthomatous granuloma or histiocytosis X, either as a monosymptomatic form of the disease or together with diabetes insipidus or other symptoms of brain involvement, bone xanthomas, or lung involvement. The nodules of xanthoma disseminatum which may be isolated, pedunculated, or packed together, appear mostly within the axillae, on the sides of the neck and the antecubital fossae. In later stages, they are scattered diffusely over the entire body. Petechial lesions may occur together with xanthoma disseminatum in the generalized form of the disease. According to Thannhauser, the nodules of xanthoma disseminatum may also appear in the mucous membranes of the mouth, epiglottis, larynx, and bronchus as well as the cornea and sclerae.

Vulvar lesions have been reported[18,19] and have given rise to such symptoms as pruritus vulvae and painful micturition. In one of the cases to be outlined below, vaginal bleeding resulted from vaginal lesions.

Hoarseness may be an initial symptom if the lesions are present in the mouth, larynx, or trachea. Hemoptysis associated with bronchial lesions has been reported.[14] Shortness of breath, cough, and cyanosis are rare symptoms of histiocytosis X and are due to interstitial pulmonary infiltration of eosinophilic granulomas. Cor pulmonale secondary to pulmonary involvement may be a late manifestation.

Moderate enlargement of the liver, spleen, and lymph nodes may occur in the chronic form of the disease and is particularly common in the acute or subacute type (Letterer-Siwe syndrome) which exists almost exclusively in children, as previously mentioned.

Anemia may or may not be present in the Hand-Schüller-Christian syndrome. When present, according to Wintrobe, it is of the nonregenerative type, leukopenia and slight thrombocytopenia may be found, or rarely a pronounced picture of myelophthisic anemia may be seen. In the Letterer-Siwe syndrome, anemia is common, thrombocytopenia is frequent, leukopenia may occur, and pancytopenia and even hemolytic anemia have been reported.[20]

Unexplained episodes of fever may occur in histiocytosis X and may be the result of softening and inflammation of either a node of the dura or an xanthomatous node in bone or involvement of the lungs. Other constitutional symptoms such as fatigue, night sweats, and weight loss are occasionally experienced.

EXPERIENCES IN SEVEN VERIFIED CASES

From this consideration, it is apparent that the manifestations of histiocytosis X can be quite varied. Experiences at this clinic are summarized in Table I which depicts the presenting symptoms, subsequent manifestations, and therapeutic problems of this disease. This chart further illustrates the variability in symptomatology. In Case 2 and Case 6 the bony lesions were apparently asymptomatic. The tendency to local recurrence and tumorlike

behavior of the disease is typified by Patient 7 who had repeated orbital recurrence of granulomas (Fig. 1). He also illustrates the therapeutic problems both from the standpoint of surgery and x-ray therapy and the efficacy of such therapeutic modalities. The tendency for "solitary" eosinophilic granulomas to occur in more than one bony site is noted in Case 3 (Figs. 2 and 3). Indeed, when one bony lesion is found, other sites of bony predilection should be investigated.

Fig. 1.—Patient 7. This photo was taken in January, 1950, prior to right orbital decompression, and illustrates the marked degree of exophthalmos. A left ocular prosthesis is present.

"Idiopathic" diabetes insipidus should make one suspicious of future obvious eosinophilic granulomatous manifestations as are suggested by Case 1 and Case 4; both of these patients developed diabetes insipidus before the diagnosis of histiocytosis X was demonstrated by skull roentgenograms. Finally, the chronicity of the disease is demonstrated in Patient 7 who has had the disorder for 17 years and Patient 4 who had had a follow-up of 12 years.

DIAGNOSIS AND PROGNOSIS

Concerning the diagnosis of histiocytosis X, it is evident that this disease may simulate a great variety of disorders. It certainly may have to be dif-

ferentiated from neoplasms involving brain, orbit, and bone in various sites. The disease may behave like a chronic infectious disease such as tuberculosis, especially when there is pulmonary involvement and symptoms of cough, night sweats, and weight loss. Furthermore, histiocytosis X may be considered in the differential diagnosis of collagen diseases such as periarteritis nodosa, sarcoidosis, Hodgkin's disease, and other lymphomas, pneumoconiosis, amyloidosis, and so forth. The disease may be more readily thought of when certain characteristic combinations of signs (for example, diabetes insipidus, exophthalmos, multiple bony lesions, skin lesions, and so forth) exist. The diagnosis, however, ultimately depends on histologic examination of involved tissue. The recent Johns Hopkins Hospital study[21] in which the manifestations, course, and prognosis of 40 cases of this group of diseases are studied, emphasizes the fact that the prognosis is far better than has previously been considered. In this entire group of 40 cases, one of which was followed 46 years, the mortality rate was only 15 per cent.

OL.
6
957

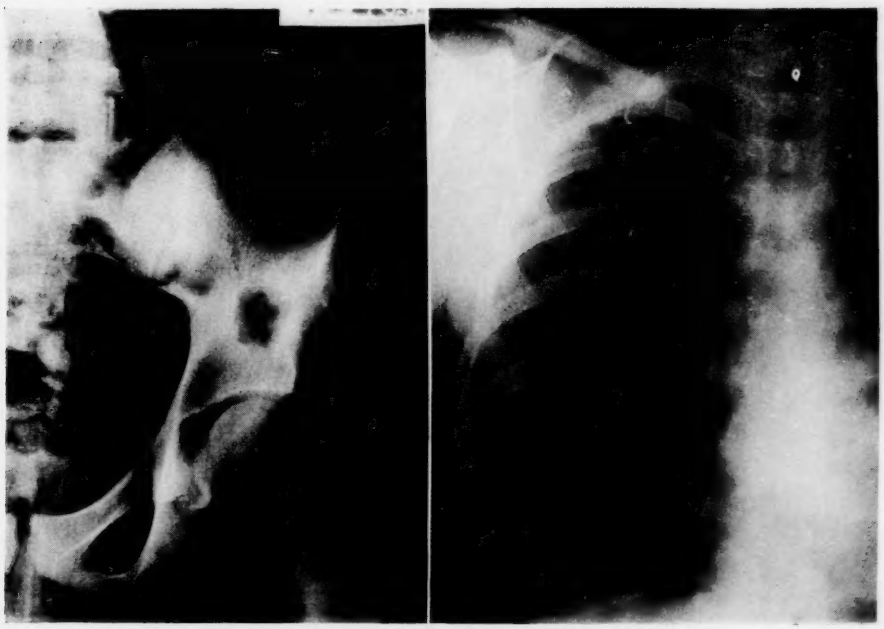

Fig. 2.—Patient 3. An osteolytic lesion of the left ilium may be seen.
Fig. 3.—Patient 3. The osteolytic lesion of the second right rib is to be noted.

SUMMARY

Experiences with 7 examples of histiocytosis X in adults are cited to illustrate the variation in symptomatology, problems in therapy, and chronicity of this disease.

TABLE I. EXPERIENCES WITH HISTIOCYTOSIS X IN ADULTS

CASE	AGE AT ONSET AND SEX	INITIAL SYMPTOMS AND/OR SIGNS	SUBSEQUENT MANIFESTATIONS	PATHOLOGIC BASIS FOR DIAGNOSIS	SURGICAL TREATMENT	X-RAY THERAPY
1	33 F	Pain in right ear, January, 1955 Thirst and polyuria January, 1955	Drainage from right ear, x-ray findings of bony defect of right mastoid process, May, 1955 Recurrence of mass behind right ear, February, 1956	Mastoid biopsies	Mastoid exploration, May, 1955 Revision of mastoidectomy, June, 1955 Biopsy of right retroauricular mass, February, 1956	1,300 r to pituitary and 840 r to right temporal bone, June, 1955 1,500 r to right temporal bone, April, 1956
2	48 M	Irregular area of bone destruction in left parietal region on skull films Chronic alcoholic with paranoid tendencies Head injuries		Parietal bone button	Removal of parietal bone button, April, 1948	
3	19 M	Pain in left hip with limp Tenderness over left ilium; x-ray findings of osteolytic lesions of left ilium, 2 cm. above acetabulum, 1949	At follow-up routine chest x-ray in 1950 demonstrated osteolytic lesion of second right rib	Iliac tumor rib lesion	Excision of iliac tumor, 1949 Excision of rib, 1950	
4	49 F	Skin lesions of thighs and arms, 1944 Skull x-rays negative, 1948	Diabetes insipidus, 1945 Vulvar pruritus and swelling, pain on micturition, finding of ulcerated vulvar lesions, 1952 Movable skull mass, skull x-rays showed punched out lesions, also lesions of pelvic bones, 1952 Intermittent episode of fever, 1952 Vaginal bleeding from vaginal lesions, 1955 and 1956	Biopsy of vulvar lesions and scalp mass	Removal of clitoris and labia minora, 1952	2400 r to skull lesions and pituitary with subsequent improvement of diabetes insipidus and lessening of pitressin requirement with improvement in skull lesions, 1952 and 1953 1,500 r to vulvar region, 1955 and 1956 with improvement in vulvar and vaginal lesions

VOL 6 1957

5	52 M	Pain in right thigh with localized area of tenderness to palpation; x-ray revealed destructive lesions of right femur 15 cm. below greater trochanter, 1942		Femoral curettings	Curettage and cauterization of femoral lesion, October, 1942	1,200 r to thigh postoperatively
6	56 F	Neurotic patient with numerous complaints of pain in neck and throbbing in head Skull films showed area of cystic destruction in occipital bone		Biopsy of granulomatous lesion in occipital bone	Excision of lesion, occipital neurectomy and arteriectomy, May, 1943 No cessation of symptoms probably not due to lesion	
7	19 M	Nasal obstruction and epistaxis due to nasal granulomas, 1939	Exophthalmos, left eye, 1941 Exophthalmos and decreasing visual acuity, right eye, 1950 Skull x-rays showed large tumor mass involving entire sinus region with cystic type lesion in left antrum Swelling, left zygoma region and mass beneath right eye, 1951 Corneal ulcer, May, 1953	Granulation tissue of right antrum and right orbit	Nasal excision of granulomas, 1949 Removal of left retro-orbital tumor, 1944 Evisceration of left eye, 1944 Anterior ethmoidectomy, 1947 Freeing of lid adhesions, right eye, 1947 Exploration of right maxillary sinus and right orbit, 1950 Right orbital decompression by Naffziger procedure, 1950 Tumor tissue removed from right orbit, 1953 Lacrimal sac removed, 1953	1,500 r to right orbit, 1950; 300 r to right orbit, June 1951 1,000 r, right orbit, September, 1951 1,200 r to right orbit, October 1952 1,500 r, right temporal area, March, 1953

Histiocytosis X may now be considered along with tuberculosis, syphilis, neoplasia, lymphoma, sarcoidosis, and collagen disease as a disorder with protean manifestations.

The organs or systems chiefly involved are bone, brain, lung, skin, reticulo-endothelial system, and certain mucous membranes.

The etiology of this group of diseases is unknown.

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VOL 6 195

CONTRIBUTIONS OF PSYCHIATRY TO THE INSTITUTIONAL CARE OF AGED AND CHRONICALLY ILL PERSONS

ALVIN I. GOLDFARB, M.D.*

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OL.
6
957

INTRODUCTION

IN THE growth of our civilization, measures beneficial to health and welfare were first supported by ecclesiastical philanthropy. Later, such measures were recognized as necessary for the preservation of social order and were taken over by municipalities or nations. At present, the perpetuation and improvement of health and welfare measures is regarded as its right by the general population. In the Middle Ages, asylums grew from the congregation of sick and needy travelers, the aged, the insane, and the criminal in places maintained by religious and lay charitable orders. When the growth of medical knowledge made possible addition of meliorative and curative methods to the hospitality extended to these people, the places of refuge and shelter developed into the hospitals we know today: sites of activity for the treatment of the sick.

There has always remained a group of people with diseases resistant to treatment. This hard core of sufferers makes up the population of many types of institutions for long-term care. In the past, even as today, along with persons whose maladies resisted all known meliorative methods, are mingled others who remain because of neglect or ignorance, because of social pressures based on fear and anger, or because they have no place to go.

Now, midway between the community and the mental or general hospital are homes for the aged and infirm and institutions for the chronically ill. They receive patients from the general hospital or from the community who cannot return to or remain in their homes because they lack the physical, mental, social, or economic resources to do so. For younger persons such institutions may provide rehabilitative procedures designed to return them to the community. For older persons measures may be instituted to help them remain productive as long as possible within these homes and to prevent or to defer their transfer to a mental hospital. While the mental hospital, even for the aged, should logically be looked to as a place of active treatment from which the patient is returned, in actual practice this is often not the case. Mental hospitals have in many instances become domiciles for terminal custodial care for which they may not be

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*Chief, Department of Psychiatry and Neurology, the Home for Aged and Infirm Hebrews, New York, N. Y.

well designed or staffed. These circumstances are part of the reason for increased growth of interest in the provision of more complete services, including psychiatric attention, in homes for aged persons.

For seven years there has been active development of a psychiatric service in a Home for the aged in which the goal has been to maintain aged persons within its walls in active relationship to the general community, with a maximum of freedom, comfort, dignity, and, where possible, some productivity. It has been of great interest to see that as the amount of psychiatric aid available increased, as psychiatric techniques of treatment improved, as the home's staff acquired more psychiatric understanding, the transfer of cases to mental hospitals dropped sharply, and patients who would formerly have been considered intolerable, unmanageable, or risky were well handled without locked doors or barred windows and with relatively little augmentation of nursing and medical care. Some details of these circumstances appear worth reporting to others interested in the problem of institutional care for aged persons.

THE INSTITUTIONAL SETTING

The Hospital and Home for Aged and Infirm Hebrews of New York, in which the psychiatric services have evolved, houses about 900 residents in two main units which include various types of facilities—rooms, dormitories, and infirmaries as well as two hotel-style apartment houses. The number of persons in each division is tabulated in Table I.

TABLE I. NUMBER OF PERSONS IN LIVING ARRANGEMENTS

	APT. HOUSE	ROOMS	DORMITORY	INFIRMARY	TOTAL
Central House (Manhattan)	168	122	158	63	511
Kingsbridge House (Bronx)	0	130	111	139	380
Total	168	252	269	202	891

Home care: 94 Home service: 5

The variety of living arrangements permits the admission and maintenance of a heterogeneous group of persons over 65 years of age. There are long waiting periods for admission ranging from several months to several years depending upon time and circumstances. Those facilities which provide maximal protection, supervision, nursing, and medical care appear to be generally in greatest demand. Persons who are relatively sound mentally and physically may be admitted to living facilities which require personal strength and responsibility. They may later be transferred to less taxing environments in which there are increasing amounts of supervision and care should they decline physically and mentally. This leads to increasing need for expansion of custodial and protective services. Acceptable applicants must be admitted directly to the units where it seems that

their needs can best be met; the decision is made on the basis of the evaluation of the medical, the social service, and the administrative staffs.

In all units the available facilities and the organization of staff are intended to encourage maximal possible self-reliance. There are aids toward participation in work, hobbies, group socialization, club participation, and religious worship. There are the usual movies, radio, television, periodicals, library, and diverse recreational facilities. The supervision available ranges from that of the "housemother" type in the apartments through modified custodial and skilled nursing care in the dormitories to complete nursing care with close medical supervision in the infirmaries. Also, each resident is followed by a social worker who in many respects acts in loco parentis. All this places within reach of every resident a number of responsible and skilled staff workers who are of continuous or potential aid to him in the solution of social, economic, and physical problems. The totality of influences comprises for many residents what amounts to a psychotherapeutic program in which planned or intuitively adopted staff attitudes play a paramount role. The wide variety of living arrangements possible, the multiplicity of services available, and the sound medical care basic to all, contribute to the residents' physical comfort and protect them from undue hardship and pain.

DL.
5
957

THE CASE MATERIAL

The majority of residents in the Home are in the eighth to ninth decade of life; the youngest referred for psychiatric care was 63 years of age at time of referral. With one or two exceptions, all are Jewish. Relatively recent "refugees" who left Europe in the late 1930's or when they were already advanced in years comprise 31.3 per cent of persons in the Home; persons who came to the United States when in their teens or early maturity make up 48.6 per cent. The number of native-born Americans is smaller—20 per cent. (Figures based on 1952 census.) The life experiences of the persons in the Home have differed widely in detail but all come from that cultural framework familiar to us as "western."

Persons were usually referred for psychiatric treatment by personnel of the Home because they constituted problems of management. Argumentative, rebellious, demanding, complaining, relatively immobilized, actively or passively sabotaging, querulous, openly depressed, potentially or actually suicidal, and assaultive, abusive or threatening residents were the most common referrals by the doctors, nurses, social workers, and administrative officers of the Home. For a resident patient to request psychiatric assistance because of his own mental suffering was a great rarity. A great many appeared to be obviously seeking out a supportive personal relationship by way of their disturbing behavior or through somatic complaints. Residents who provoke anxiety or resentment are most commonly referred; patients who suffer quietly, who have problems that do not arouse anxiety or resentment, who do not require that they or those around them be protected are not often referred to the psychiatrist in the Home; nor are those who provoke pity, compassion, or who seem to need straightforward rational counselling which yields them special attentions. However, once referral has

been made, a fair proportion spontaneously continue to seek out the psychiatrist and to perpetuate the interviews, or to be returned quickly on the slightest suspicion of trouble.

CASE ILLUSTRATIONS: EARLY EXPERIENCES

In the past, the Home attempted to help to the best of its ability but eventually had to transfer certain needy, sick, or mutilated persons who constituted serious management problems because they were disturbed or disturbing. Many of them, like the following patients, became wanderers in search of services, or were at best problems handed on to another supervisory organization.

CASE 1.—R. M., a 72-year-old native American widow, was admitted to the Home in 1950 because she was sick, lonely, and there was no friend or relative with whom she could live. One eye had been enucleated as a result of glaucoma, and the right breast had been amputated because of carcinoma. She was garrulous, overactive, bossy, and from time to time was convinced that people disliked her, talked about her, and wished her ill. At these times she was volubly angry, critical of the Home and its staff, and eager to leave. Occasional interviews with the psychiatrist were opportunities for her to aggrandize herself, deny the failure of her powers, and assert her great helpfulness to other residents. To the latter she was actually aternately oversolicitous and angrily critical, provoking them by her interference in the first place and causing them to avoid her in the second. Social workers and nurses, when informed that her hypomanic state hid a depression, were sympathetic and responded to her masked dependency with a protective attitude which enabled her to remain in the Home for 2½ years. At the end of that time, at her insistence, she was helped to find a room in the community where she remained for 6 months and then entered a city hospital because of a bowel disturbance. After 3 months in the hospital she went to a boarding home. After about 6 months there, she applied and was admitted to another home for aged persons.

Comment: The interesting feature in this case of a friendless, indigent, physically impaired widow is the existence of a mild hypomanic state in a woman of 72 years who had only the slightest indication of a chronic brain syndrome. The indications for specific treatment in or out of a hospital were not completely clear, and there was reluctance on the part of the staff to recommend hospitalization for mental illness. It might have been possible to maintain her within the Home if special nursing care had been available. She remains a needy, sick wanderer because we could offer only limited psychiatric assistance. She has no relative or friend who can play a responsible firm part in her guidance, and she is a problem passed on to someone else.

CASE 2.—M. K., a widow, a native of France, claimed she was 69 years of age but was reported to be 75 years old when she entered the Home in 1950. She had lived with her parents until they died and then, when 38 years old, married. Four years later her husband died and she went to visit a niece with whom she remained for the next 20 years. Shortly after being turned over to the Home by the niece, she evidenced clearly hostile and domineering trends. She threatened to strike residents with her cane and actively lashed out from time to time if they did not please her. When enjoined to desist, she threatened to commit suicide. The psychiatrist found her aggressive, argumentative, indignant about the persecution she suffered at the hands of "those refugees." She railed about sharing a room, about snorers, and about a variety of other things. Her attention span was limited and her memory poor, but most of all she had little respect for the rights of others. The psychiatrist tried to help her see that she would forfeit her rights to residence in the Home unless she were more agreeable. She was seen by the psychiatrist for a few months at intervals of about 10 days. She was ingratiating and flirtatious, often came to see the therapist

without appointment, and always seemed reluctant to terminate interviews. Her excitability and her frequent minor altercations led to the administration of sedatives by the house physician. The psychiatrist noted that these increased her confusional state. When the barbiturates were decreased in amount she was more easily managed and was maintained in the Home for 18 months. However, coincident with an acute bronchitis, she became continuously hyperactive, noisy, and disoriented. She slapped a nurse and shortly thereafter was transferred to a mental hospital. A follow-up report, 6 months later, indicated that she was quiet, lucid, and desired to return to the Home, explaining that she "was sick before and would not act that way now." Two years later she died in the mental hospital.

Comment: This 75-year-old widow had a lifelong dependency on her family. A hostile, assaultive trend aggravated by sedatives and infection brought to an end her dependency on the Home where, with the help of psychiatric supervision, she had been maintained for 18 months. If sedatives which were not cortical depressants had been available at that time, she might possibly have been maintained longer in the Home. She was transferred to a mental hospital with adequate reason but from a point of view which was based on overreaction to assaultive behavior. She lived in the mental hospital for 2½ years, considerably longer than do many persons after such transfer. These years, if spent in the Home with or without a brief sojourn in a mental hospital, would probably have been happier for her.

OL.
6
957

These 2 patients are examples of about 6 persons per year, on the average for the 15 years 1942 to 1956, who, of over 900 of our residents, were considered such a danger to themselves or to others or were considered so disturbing to the Home community that transfer was arranged. They were returned to their families, to the community, or were sent to mental hospitals. Many died within a short time after transfer. Growing psychiatric facilities appear to be one major factor in making possible longer residence of such persons within the Home. The prolongation of residence of emotionally disturbed persons provides opportunity for the staff on all levels to become acquainted with the aims and methods of the psychiatrists.

CASE ILLUSTRATIONS: RECENT DEVELOPMENTS

The Socially Disturbing.—The maintenance of obviously emotionally disturbed patients within the Home was undertaken first with reluctance; this was followed by increased willingness to tolerate and deal with behavior disorders of the aged residents when understanding of basic psychodynamic principles became operative. It then became possible to maintain within the Home persons with even greater emotional disturbances than those described above. Only one transfer to a mental hospital for permanent care has been necessary in the past 2 years.

The following are examples of persons who benefited greatly by remaining in the Home in spite of behavior which at many times threatened to divorce them from it.

CASE 3.—F. H. was born in Germany and came to the United States in 1906. She was an obese woman with hypertensive cardiovascular disease when she began to plead for admission to the Home in 1941, at the age of 57. Her husband, then 75 years of age, had already been in the Home for 12 years, and she wished to be with him. She was encouraged to remain outside, working

as a practical nurse, until she was 60 years old. Her two children were mentally defective; she herself appeared to be of low intelligence, although this was not later verified. From the moment of admission she was angry, sullen, bitter, and behaved like a martyr. She was domineering and had difficulty with her roommates but was very attentive and helpful to her sick husband. Because of her belligerent attitude to other residents, she was asked to see the psychiatrist, but refused, and the psychiatric service followed her course through consultations with social service and the administration of the Home. In 1953, when she was 69 years old, she suffered an attack of mild cardiac failure and withdrew to her room. She refused to take anything but buttermilk. She was admitted to the infirmary where, when seen by the psychiatrist, she was hostile and suspicious. She was evasive about her withdrawal to her room, insisted that it was not because of illness but because her husband called her names. This was in line with previously noted trends; whatever she was unable to do she tended to blame on her husband; whatever misfortune befell her she regarded as the result of her mate's neglect, abandonment, or ineffectuality. She was seen sporadically by the psychiatrist. She had intermittent attacks of mild cardiac failure which finally led to her permanent residence in the infirmary. In 1955, her husband died, and soon after she became agitated, complained that her room had been taken away from her, and complained that we wanted her to leave. She was depressed, ate little, said her food was poisoned, and complained of mistreatment. Her sensorium was intact throughout. No medication was of benefit. A satisfactory arrangement for electroshock treatment could not be worked out. In the fifth month of her illness she required tube-feeding. At that time chlorpromazine and azacyclonol hydrochloride were given in combination. Within a week she was eating, was quieter but still delusional, angry, and convinced she was being poisoned. There were occasional auditory hallucinations. In the next 3 months improvement was slow but constant. She began to take interest in the therapist who saw her at weekly intervals. She began to eat well, her delusions subsided, and now, 11 months after the beginning of this acute episode of melancholia, delusions, and paranoid ideas, she is critical, occasionally uncooperative, and much the same as she was for the years preceding her husband's death except that she is no longer obese, to her heart's good fortune.

Comment: The future of this woman is uncertain. Although chronically on the border line of a psychosis for many years, she managed fairly well, helped to care for her husband, and, despite grumbling and complaints, lived a fairly normal life in a community of older persons for 10 years. When her husband died and her heart failed progressively, she experienced an acute psychotic episode. She was cared for within the Home by the medical and nursing staff and improved without the use of electroshock treatment. She illustrates that a psychotic patient can be maintained and treated by interested and cooperative personnel within an agency which at one time approached even simple behavior problems with timidity.

CASE 4.—J. S. is the younger brother of the third patient. He, too, was born in Germany from which he fled to the United States with his family in 1940. Most pertinent in his past history was that he had applied to the Home 2 months after the death of his wife, who seemed to have managed all his affairs and to have protected him as a parent does a child. He had been unable to continue even simple work after his wife's death and before his admission had to be financially supported by his daughter. Six years ago, a few months after admission to the Home, he had frequent quarrels and explosive outbursts of anger. One of the quarrels ended in a physical fight. He was also suspected of minor thievery. The patient was obviously frightened on being referred to the psychiatrist for help. He was ingratiating, almost fawning. When he spoke about a recent quarrel he became agitated, excited, and angry, but protested vigorously that he was himself peaceable, avoided quarrels, and, in fact, retreated when confronted by aggression. He regarded referral to the psychiatrist as a punishment and a threat to his status as a resident of the Home. The psychiatrist mildly agreed that his quarrelsome manner placed him in jeopardy. A facial tic, previously present, became grossly accentuated during the interview. He was informed that the therapist would remain interested in him and was asked to return to tell about any difficulties

that might occur rather than to try to adjust them on his own. It was the psychiatrist's impression that this man, of borderline intelligence and with an obsessional type of character disorder, had been able to make a marginal social adjustment when directed and controlled by his wife. It was predicted that there would be an occasional minor flare-up of verbal aggression involving other residents but that control could be effected by occasional visits to the psychiatrist and that he could be maintained in the Home. The social service, nursing, and administrative staffs were reassured on this score, and the patient was seen about once a month for several months. He was seen subsequently whenever there were indications of undue hostility. He has remained fairly well behaved. He now works as errand boy for disabled patients.

Comment: This man, who incidentally has severe psoriasis and eczema, is one in whom there were threatening eruptions of paranoid trends similar to those noted in his sister. He was stabilized, although not improved, and helped to remain as a working resident in a Home for the Aged without great expenditure of psychiatric time and effort. Before coming to the Home he was able to carry on in the community so long as he had a motherly wife to protect him. In a well-regulated institution wherein there are figures he can regard as authoritative but protective, he is capable of working with a minimum of supervision and without restraint. That he was not summarily dismissed when his quarrelsome and assaultive trends became clear was a psychiatric decision based in part upon the role another resident played in the incident which might have led to his transfer. A description of the latter, who also became a psychiatric patient follows.

VOL.
6
1957

CASE 5.—N. L., whose birthplace was London, England, was seen in emergency psychiatric consultation at the age of 71, because he had been in an altercation ending in fisticuffs with J. S., described before. He had a parasympathetic block for peripheral vascular disease in 1943, a herniorrhaphy in that same year, a prostatectomy in 1945, and in 1947 and 1949, respectively, a left and right lumbar sympathectomy. Under stress of progressive cardiovascular disease and failing physical powers, N. L. had steadily become more despondent and apprehensive. He appeared to be irritable and resentful that the Home was not providing him with a more pleasant life. He felt neglected physically although he was given a large amount of good medical care. In every whining word and petulant gesture he appeared to be spoiling for a fight to prove that the world was treating him abominably and to justify his perpetual pouting and righteous indignation. He had multiple aches and pains and a long list of grievances. He appeared to have provoked Mr. S.'s attack to prove that "men are beasts." His somatic complaints were heard by the psychiatrist, and he was enjoined to avoid quarrels with Mr. S. Four days later when seen again he was more cheerful although on that morning, as on other occasions, he had spoken of killing himself. Such remarks were made in a manner calculated to impress us that he should receive more benefits and greater consideration. He established a complaining, grumbling relationship with the therapist to whom he came willingly, often on his own request, for additional discussion of his physical symptoms.

Comment and course: This man behaved like a querulous, whining lion—a 110-pound fellow described by the social worker when he applied for admission to the Home, as a meek, mild, submissive, and complacent person with "big blue eyes." He presented many severe psychoneurotic symptoms of long standing, including hypochondriasis as a habitual mode of hostile expression. A diagnosis of simple schizophrenia could have been equally well supported, and he would have qualified for admission to a mental hospital. In the Home he was closely followed for 4 years through constant weakness, active physical illness—prostrations with bacteremia, two mild strokes, contractures, bursitis, arthritis,

and progressive arteriosclerosis and hypertensive cardiovascular disease as well as many emotional upsets. Each of the emotional disturbances was quickly resolved after a few psychiatric interviews. These gave him a person to defy, to flout, following which his behavior improved. At present, a friendly chatty relationship with a kindly precise but jokingly maternal and authoritative medical secretary feeds his sense of importance and his desire for mothering, while it also serves as a kind of thumbing of the nose at the psychiatrist with whom he maintains a good but very superficial relationship.

The history of social and sexual isolation in this man indicated early acquired pervasive inhibitions; his behavior in the Home as well as his associational flow in conversation indicated that, like so many other fear-ridden ineffectual men, he had contempt for himself. He had regarded himself as weak and a cripple even before infirmity was notable; feeling fragile and disabled, he had pictured himself as not manly, to wit, feminine. He was sensitive and easily hurt, fearful of men, and on guard and evasive. He was quarrelsome, whining, and petulant, in defiant denial of the feelings of helplessness which simultaneously drove him to seek protection. Maintenance of the psychiatrist-secretary team treatment has been paralleled by absence of further serious incidents. This case is an example of some of the special types of teamwork, often inadvertently come upon, which can help to keep even seriously disturbed persons within the community.

The following married couple are a further illustration of persons probably eligible for mental hospital care who could be kept in the Home.

CASE 6.—Mr. and Mrs. J. R., both natives of Germany, were admitted to the Home Care* program of the institution when they were 73 and 57 years old, respectively. Because of their poor health, both desired the guarantee of future admission to the institution which the Home Care program provides. Mrs. R. was obese and had gastrointestinal complaints related to her overeating; chronic cholecystitis; and advanced hypertensive cardiovascular renal disease. Mr. R. had suffered a "mild stroke" which made it impossible for him to continue work. They had migrated from Germany after many hardships and in this country had worked hard to support themselves. For a year, Mrs. R's worry about her illness increased, but her concern about her husband's health was even greater. She overprotected him, dominated him, and protested guilt about leaving him alone, although she seemed to do so at every possible opportunity. Her somatic complaints increased greatly in number and intensity, she was tearful and depressed, but she resented a doctor's implication that she was nervous and in need of psychotherapy. When her husband announced his decision to enter the Home because of his declining health a day or two after she had dutifully attended the funerals of two acquaintances, she took an overdose of sleeping pills. She was admitted to a hospital for care. Her husband excitedly had her signed out against the advice of the psychiatrists. The couple were erroneously convinced that they had forfeited their rights to Home Care and to admission to the Home. Nevertheless, they appealed to it for aid because they were penniless and uncertain about what to do. When interviewed, Mrs. R. was self-accusatory and self-depreciative for having forfeited their Home Care status. She was depressed and agitated but denied she had actually attempted suicide. She claimed to have taken a small overdose of sedative by mistake. She felt overwhelmed with guilt. She spoke of the loss of family and friends, and of her marriage at 27 years of age, at the insistence of her family, to this well-established man so much her senior who was supposed to take care of her but now was so impotent. Her conversation revealed that since her husband's decline she had sought

*The Home Care program is provision of certain services, not including medical care, while the persons remain in their own domiciles.

protective care, but pride required that she hide this from herself and others. She had settled chiefly on the technique of appearing strong and of service to others—her husband, club members, friends—to earn, deserve, and attract special attention and care while appearing to be protective and independent. Her suicidal attempt had been in a context of limited opportunity to deny helplessness by proof of worth. When the psychiatrist suggested that she could resume her status on Home Care and that she might come to see him regularly if she wished, thus implying she was considered worth while and respected, she brightened at once and indicated that if she had had such help from a doctor for her illness previously she might not have made the mistake of the sleeping pills. She then placed her need on the basis of her gastric distress, her excessive weight, and her heart trouble. She and her husband were maintained on Home Care for 3 years during which time she was seen at weekly intervals for 4 months, then once a month or less. As her husband grew worse and worse, she complained more and more bitterly about his decline and her concern obviously overlay chronic resentment. She accepted admission to the Home intramural program, saving her face by regarding it as a need of her husband's and done for his sake alone. Frightened about her illness and discontented with her lot of living in a Home for the aged when only 60 years old, she centered more and more around her concern for her husband's health. Interviews alternated between being times of special requests for change of medication, diet, and regime for herself, and pleas for explanation of and help with her husband's dysphagia, dysphonia, lethargy, and excitability. The pattern of treatment continues unchanged after 3 years. Mrs. R. is unable to attend 3 months running without bringing a gift of her own making—ash tray, rug, or doll—to the psychiatrist to prove her gratitude and bolster her sense of pseudo independence.

VOL.
6
1957

Comment: There are persons like Mrs. R. who although in need of protective care may, in a hospital or institutional setting, feel regimented, trapped, and imposed upon and as though held against their will. They rail at their captors and at themselves for the turn of events, for the arrangement for which they feel some responsibility, and at the state of the world which permits such injustices to befall them. A pre-existing sense of helplessness in them has been accentuated by illness and losses that go with age and is reinforced by the rule, regulation, regime, and order of an organized hospital unit.

Mrs. R. illustrates that a frightened, helpless female hemmed in by circumstances and disease may feel unwomanly, useless, not of service, and may vainly try to hide this from herself. This she did by means of emphasis on her past services, her past strengths, and excellences as wife or mother, as well as by present-day feverish work for and concern about others, especially those she most wanted to have take care of her. At the same time she became frightened by the seemingly masculine characteristics of her behavior, especially as it was emphasized by contrast with her progressively weakening husband. Resentment against the husband for departing from the protective roll she required but denied needing was directed against doctors who were unable to improve his status. As the husband grew progressively worse and his brain damage increased, she went through periods of despondency and complaint.

On the other hand, there are persons like Mr. R. who come to the refuge the Home affords with frightened reluctant tentativeness, persons in desperate need of protection who nevertheless feel threatened by the asylum it can provide. Admission may paradoxically gratify some of these persons. The regulations they feared may remove personal need for making decisions, for proving their worth, and relieve them of continued work and competition. They welcome a state of enforced dependency which resolves their problems and frees them from their sense of helplessness and its attendant anxiety. If given duties or special

privileges, they may react badly and become anxious because they may feel punished, abandoned, and helpless.

Mr. R., in contrast to his wife, accepted this state of dependency, thereby increasing Mrs. R's resentment and threatening her own feeling of independence. Each requires continuous medical-psychiatric support and they remain a time-consuming pair.

These cases illustrate that persons seriously ill from a psychiatric point of view can be maintained in an institution not generally regarded as providing intensive psychiatric care.

The Disturbing Who Require Special Nursing Care.—The extension of psychiatric services to the care of patients who are argumentative, threatening, or suicidal can make continuation of residence in the Home possible for many who would have had to leave. The provision of additional personnel for special nursing made possible improved care for a different type of disturbed persons. For convenience, they were placed in a 4-bed ward. This was staffed by kindly, sympathetic attendants on a 3-shift basis.

CASE 7.—A. M., a 73-year-old native Puerto Rican woman, had been in the infirmary of the Home for one year because of an ununited hip fracture. She had an acid tongue, believed she was being persecuted by the nurses and medical staff, cursed noisily, was excessively demanding, and required a great deal of supervision. Ordinarily she would have been transferred to a mental hospital. Instead she was transferred to the 4-bed ward where her regime was supervised by the psychiatric staff. She had an occasional interview with the psychiatrist, received medication as needed, and complete medical care. She was manageable and relatively quiet under the special nursing arrangement. Her cursing persisted and her paranoid ideation remained as before, but she was not disturbing to other residents or to personnel. The patient died of bronchopneumonia after 10 months of such care.

CASE 8.—B. S., an 80-year-old Hungarian-born woman, with hemiplegia of 2 years' duration, slowly declined in strength despite rehabilitative procedures while her memory slowly declined as well. She suffered pain of thalamic type which medication could not completely allay. She complained constantly of pain, was agitated, and called out so persistently for attention and relief that she was very disturbing for other residents on the ward. The patience of the regular infirmary staff was exhausted. She was transferred to the 4-bed ward where, under psychiatric and medical supervision, she became quieter and less demanding. She remained until her death of coronary thrombosis 4 months later.

CASE 9.—A. L., a 66-year-old native German woman, developed rapidly progressive memory loss, was panicky, restless, agitated, and wandered about in a confused way. She refused to eat and lost weight and strength. The clinical picture was one of Alzheimer's disease. Transfer to the special nursing area made possible continuous supervision, effective use of tranquilizing medication, and tube-feeding when necessary. This, together with medical care to prevent infection, enabled her to remain in the Home for 15 months after her rapid decline began. She was then transferred to a mental hospital.

Comment: The provision of accessory nursing services have indicated that active, well-supervised treatment of very acutely disturbed and disturbing persons who show promise of recovery, or whose demise is close, is possible in an old-age home. Transfer to another institution from the area to which persons have come to spend their last years is often viewed as a cruelty by the patient, their families, other residents, and the personnel of the Home. That these sick persons were not transferred, or were sent elsewhere only after it was obvious that their decline could not be averted by modern care, was heartening to all concerned.

From June, 1955, to the present, less than a year, the special nursing unit has served 14 patients who have remained there for periods of 1 to 10 months. Of these, 5 improved within one month or less. Five who died remained one week, one month, two for 4 months, and one for 10 months, respectively. Four patients remain under treatment.* From this pilot study we expect to learn more about what kind of persons may profit from extra care and attention, in how long a time we may expect them to respond, and also which cases we might have tolerated a little longer rather than send to a mental hospital for terminal care. This pilot ward does not serve what are regarded in the Home as medical-nursing problems in which psychiatric aid is ancillary, that is, the toxic infectious disorders of physiologic nonsupport, the acute brain syndromes seen with infections, uremia, cardiac failure, and the like. Such delirious reactions are treated routinely in the regular infirmary.

OL.
6
957

DISCUSSION

Residents of old-age shelters are not easily categorized as "with nervous and mental disease," "chronically ill aged," or "debilitated and dependent aged." Obviously these are overlapping groups and an individual may move from one to another. Almost all persons in the Home who come to the attention of the psychiatrist's care are also otherwise chronically ill. The "nonpsychiatric" disease process present has usually played a part in determining the psychologic and emotional attitudes displayed and, conversely, psychologic attitudes and emotion have probably influenced the progress, the severity, or the symptomatology of the illness. Invalidism and care required are often determined more by the psychiatric situation than by the physiopathology. Because physical illness is common and fears about illness as well as bodily preoccupations are also common and not always unreasonable, good medical and nursing care is an essential basis to psychiatric care. Sound sensible medical practices themselves have psychotherapeutic influence; without them the psychiatrist works in a vacuum. Conversely, medical care without psychiatric understanding and orientation, in such circumstances, is often inadequate. The psychiatrist who treats the aged must himself have reasonable skill in general medicine and be prepared to use it in his practice, in cooperation with the general medical staff.

In old-age shelters the need for psychiatric care in addition to specific and supportive medical measures is great. The need is not easily met under present socioeconomic conditions. However, it is probably not being met, even to the degree possible, because of the uneasiness felt by many psychiatrists when they are faced by chronic illness in older persons. The social and economic problems of the aged and the extent and severity of their physical ills are discouraging. The amount and intensity of psychopathology which emerges under these circumstances of diminished personal and material resources is impressive and often unduly disheartening to those unfamiliar with the patterns. The very helplessness of the aged dependent, chronically ill person, by impelling him to turn for help,

*Figures are as of March, 1956.

makes possible a therapeutic relationship. Although the accessions of fear and anger in these patients may give rise to numerous problems of management frightening to hospital or shelter personnel, the reactions may respond readily and rapidly to psychiatrically oriented measures. These measures are not necessarily time-consuming. They consist in the main of reassurance and support to the patient by means of brief, even widely-spaced, interviews. The patient feels reassured and supported by the interest and ministrations of the physician; the patient not only feels safe because medical skill has been placed at his disposal but also takes special pleasure at having gained and being able to hold such a powerful ally. Possibly because these responses are so commonplace, so "primitive," and so effectively made use of even by therapists without medical skill or training, many physicians may be reluctant to utilize them as freely as they might. Even psychiatrists are often reluctant to treat their patients by means of 10- to 15-minute interviews at intervals of once or twice a week or less. Experience with aged ill patients strongly suggests, however, that a great deal can be accomplished toward relieving mental suffering, improving social behavior, and relieving symptoms of emotional overreaction by means of short, infrequent interviews or even by means of seemingly catch-as-catch-can sessions here or there on the ward or in the corridor. With some patients the absence of definite appointments and definite meeting places is desirable. They like to be sought out or to take special pride that time has been spent with them by the busy physician even though the meeting was by chance. In many instances it is a mistake to try to do a great deal in a formal manner with chronically ill, anxious, angry, or depressed patients. A word or two, a handshake, or the bland acceptance of a rebuff from such patients may have profound psychotherapeutic effects if it is consistent with the patient's emotional needs.

Efforts of this kind may require that the psychiatrist acquaint others concerned in the patient's care with the goals of therapy and its rationale. The therapist at times can feel free to point out that he does not delude himself that it is he who is always the moving force in therapy. Self-election to the healer's role by the physician does not always coincide with the patient's views or the patient's choice of who can and must help him. Staff can learn that the psychiatrist may be simply an incentive to the patient to seek out someone else, or may serve to introduce the actual therapist. The person selected by the patient as parental surrogate and from whom reassurance and support are gained may be the doctor's secretary, a social worker, the patient in the next bed, the night nurse, or an occasional visitor.

Hospital personnel usually profit from learning that sick persons may regard them as parental figures and that emotional reactions displayed to them, whether positive or negative, need not be taken personally. At times the psychiatrist may note the unsuspected delegation of a staff member to special status by a patient and can make his contribution to the patient through the other, either by supervision and guidance, or by helping the patient-delegated parental surrogate with the feelings aroused in him by the relationship.

It not infrequently occurs that the psychiatrist's interest in the patient awakens fear or anger in him which has a helpful organizing effect and which is

therefore not discouraged by the therapist. Transactions of this nature may be disturbing to members of the staff who become angry with or afraid of the psychiatrist. At times, this changes their relationship to the patient for the better. A change in attitude toward the patient for the better may come from pique that there has been psychiatric intervention or from desire to impress the psychiatrist. Because harmful attitudes to the patient may as easily stem from such competitive, rebellious, or resentful attitudes to the psychiatrist on the part of staff, staff conferences or instruction may play a significant part. At times orientation of staff is beset by many difficulties, and it becomes necessary for the psychiatrist to recognize that he must deal with staff as he does with the officially designated patients until such time as they can become cooperative members of the therapeutic team. Needless to say the psychiatrist must keep in mind the possibility that his own attitudes to other staff members may be irrationally determined or have irrational components.

In an institutional setting where relationships are superficially complex and interweaving, the psychiatric transaction is one which offers support and reassurance to residents directly and to the staff both directly and indirectly so that they are better able to work with their charges. The patient-doctor relationship may be the epitome of beneficial relationships becoming established rather than the significant relationship.

Above all, flexibility in the handling of the aged sick is of paramount importance. That they themselves may not be flexible and may have few resources for actual unaided mastery of physical and social problems becomes less frightening and discouraging when we realize that their dependency upon others can be put to very good use.

SUMMARY

Homes for the aged are institutions for the long-term care of a variety of medical problems. Exacerbation and aggravation of chronic illness commonly occurs with psychologic stress and emotional overreaction. Dramatization of illness is also common, and its use to manipulate the social environment is well known. Rational treatment of chronic disease without consideration of the psychiatric aspects is therefore impossible.

The cases cited in this paper illustrate that the care of aged persons with chronic illnesses, and of elderly individuals with unstable behavior is improved by the addition of psychiatric services. These are helpful directly through provisions of specific measures and directions, and indirectly through their effect upon staff and general morale. The direct and indirect efforts combine to augment the comfort of the residents and may be helpful in decreasing the number of transfers to mental hospitals.

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VOL 6 195

LEVEL OF MEDICAL INFORMATION AMONG CLINIC PATIENTS

ARTHUR W. SELIGMANN, M.D., NEVA EILEEN MCGRATH, M.D., AND LOIS PRATT, PH.D.

NEW YORK, N. Y.

From the New York Hospital, Cornell Medical Center, New York, N. Y.

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OL.
6
957

ALL physicians will attest to the amusing and at times appalling misconceptions among patients about their own ailments and those of their friends. One need travel no farther than the nearest cocktail party to glean material worthy of the primitive medicine man. More scientific documentation of this deficiency in patients' knowledge is provided by the studies of Redlich[1] who worked with psychiatric patients and Collins[2] who dealt with obstetrical patients.

Adequate medical care requires considerable understanding and participation by the patient at various stages of his illness. First he must decide where and when to seek help. Second, he should be able to supply accurate and relevant information to the physician about his condition, including changes that occur and effects of therapy. Third, the quality of care often depends on the extent of his cooperation with the physician in carrying out treatment. The patient's ability and willingness to participate effectively in these three phases of his care depend in part on his conception of his own condition and of medical care in general.

What then are the patient's ideas about illness and medical care? The present study attempts to determine the level of medical information about ten common diseases in a group of unselected clinic patients. This is a step in an attempt to find out how the physician can learn to communicate more effectively with his patients.

MATERIAL AND METHODS

A multiple choice, self-administered questionnaire was devised to measure knowledge about the following relatively common disorders: tuberculosis, cerebral vascular accident, stomach ulcer, syphilis, diabetes, coronary thrombosis, arthritis, asthma, menopause,* and leukemia. The questions took this form.

1. Tuberculosis of the lungs is due to:
   a. Prolonged exposure to the cold
   b. Infection with a germ
   b. Anemia and vitamin deficiency
   d. Don't know
   (No answer)

*This physiologic episode is included because it often causes symptoms.

2. The commonest symptoms of TB of the lungs are:
   a. Pain in chest after exercise
   b. Chronic cough and sputum
   c. Wheezing sounds on deep breathing
   d. Don't know
   (No answer)

3. Many patients with TB of the lungs are now successfully treated by:
   a. Vitamin injections and special diets
   b. Prolonged exposure to the sun and special exercises
   c. Antibiotics and bed rest
   d. Don't know
   (No answer)

4. TB of the lungs is best diagnosed by:
   a. Chest x-ray
   b. Observing temperature and weight
   c. Stethoscope examination of the chest
   d. Don't know
   (No answer)

The respondent was instructed to circle the letter next to the correct answer. In each disease, three or four questions were asked, one each about etiology, symptoms, and treatment. In another section, the respondent indicated which diseases he had had and which afflicted his relatives or acquaintances. He also noted his age, sex, highest school grade completed, country of birth, and length of residence in the United States. The questionnaires were unsigned to encourage respondents who might be embarrassed at their lack of information to cooperate.

THE SAMPLE

Questionnaires were administered to 214 medical outpatients during January, April, and May of 1955. All patients who appeared at the sessions when testing was conducted received questionnaires. Ten per cent failed to complete them, chiefly because of anxiety about health, faulty vision or hearing, and language or reading difficulty. The interviewers kept the sample loss down to 10 per cent

TABLE I. GENERAL LEVEL OF INFORMATION ABOUT DISEASE AMONG THE PATIENTS

PER CENT OF QUESTIONS ANSWERED CORRECTLY	NUMBER OF PATIENTS	PER CENT OF PATIENTS
0-9	13	6
10-19	8	4
20-29	11	5
30-39	23	11
40-49	13	6
50-59	31	15
60-69	37	17
70-79	51	24
80-89	22	10
90-100	5	2
Total	214	100

by reading questions to the respondents and recording the answers whenever difficulties arose.

Stability and uniformity of the clinic population were tested by examining another sample obtained months after the present study was completed. The second group, chosen in the same way and for a similar project (see tabular material in footnote), was quite comparable with regard to sex, nativity, age, and education characteristics.

RESULTS

1. *General Level of Information About Disease.*—Fifty-five per cent of all answers given to the test questions were correct. The distribution of patients by the proportion of correct responses is shown in Table I.

2. *Level of information about Specific Diseases.*—Table II shows the percentage of correct answers tabulated by disease. It is interesting that the proportion answering correctly varies from 38 per cent in the case of coronary thrombosis to 73 per cent for tuberculosis and that there is no relationship between the amount of information and the frequency of the disorder or its mortality rate. Possible explanations for this phenomenon are discussed below.

3. *Relation of Personal Experience With Disease to Knowledge of Disease.*—

a. *Patient's knowledge of his own diseases and diseases of associates:* Table III shows the proportion of persons who have had a disease who answered correctly the questions about the disease, as well as the proportion of persons with associates afflicted by the disease who answered correctly the questions about the disease.

There is a greater tendency for a larger percentage of persons who suffered from a given condition to answer correctly the questions about it than is true of the group as a whole, but persons with acquaintances who have had a particular disease show more striking and statistically significant superiority to the entire group.

	PRESENT STUDY SAMPLE (%)	50 PER CENT RANDOM SAMPLE* (%)	LATER STUDY SAMPLE (%)
Sex			
Men	32	39	29
Women	68	61	71
	100%	100%	100%
Nativity			
U. S. born	67	55	71
Foreign born	33	45	29
	100%	100%	100%

*During one month, every second patient who came into the clinic was taken into a study sample.

TABLE II. LEVEL OF INFORMATION ABOUT TEN DISEASES AMONG THE PATIENTS

DISEASE	AVERAGE PER CENT OF QUESTIONS ANSWERED CORRECTLY*
Tuberculosis	73
Diabetes	71
Syphilis	63
Arthritis	57
Change of life	53
Asthma	52
Stroke	51
Stomach Ulcer	44
Leukemia	40
Coronary thrombosis	38
All diseases	55

*The per cent of correct answers to the tuberculosis questions is significantly greater (at the 0.05 level) than the per cent for 7 of the 9 other diseases. Similarly, the per cent of correct answers to the coronary thrombosis questions is significantly lower (at 0.05) than the per cent of correct answers about 7 diseases. Further evidence for the reality of the differences is found in the fact that a replication of the study on a new sample 6 months later produced very similar results.

TABLE III. LEVEL OF INFORMATION ABOUT PARTICULAR DISEASES AMONG PERSONS WHO HAVE HAD THE DISEASE, PERSONS WITH ACQUAINTANCES WHO HAVE HAD THE DISEASE, AND IN THE SAMPLE AS A WHOLE

DISEASE	AVERAGE PER CENT OF QUESTIONS ANSWERED CORRECTLY AMONG*				
	PERSONS WHO HAVE HAD THE DISEASE	NO. OF CASES	PERSONS WITH ACQUAINTANCES WHO HAVE HAD THE DISEASE	NO. OF CASES	ALL RESPONDENTS
Tuberculosis	91	(11)	86	(60)	73
Diabetes	82	(26)	81	(86)	71
Syphilis	73	(22)	73	(11)	63
Arthritis	51	(61)	71	(62)	57
Change of life	59	(78)	71	(73)	53
Asthma	81	(16)	66	(68)	52
Stroke	61	(12)	66	(69)	51
Stomach ulcer	†	†	†	†	44
Leukemia	25	(4)	64	(26)	40
Coronary thrombosis	48	(14)	54	(34)	38

*There are no statistically significant differences between the level of information about a given disease of those who have had the disease and the sample as a whole. Had there been a larger number of persons with the various diseases some of these differences might have been significant.

The differences between the level of information of those whose associates have had a given disease and of the sample as a whole are significant at the 0.10 level for these diseases: tuberculosis, arthritis, change of life, asthma, and stroke.

†Question not asked.

b. *Patient's knowledge in relation to multiple experiences with disease:* Table IV shows that there is no relationship between the number of diseases an individual has had (of the nine about which respondents were questioned) and the extent of his information about all diseases. Persons who had had none of the diseases (Table I) gave as many correct answers as those who had had four or more. This table also shows, however, that the more diseases the respondent's associates have had, the more correct answers he gives.

4. *Patient's Knowledge in Relation to Educational Level.*—Table V demonstrates that an individual's information about disease correlates significantly with educational level attained. These findings differ from those of Redlich.[1] High

TABLE IV. LEVEL OF INFORMATION ABOUT DISEASE BY NUMBER OF DISEASES THE RESPONDENT HAD HAD, AND BY NUMBER OF DISEASES HIS ASSOCIATES HAVE HAD

NUMBER OF DISEASES	PER CENT OF QUESTIONS ANSWERED CORRECTLY BY:*		NUMBER OF CASES†	
	THE RESPONDENTS' OWN DISEASE EXPERIENCE	THE DISEASE EXPERIENCE OF THE RESPONDENTS' ASSOCIATES	OWN DISEASES	ASSOCIATES' DISEASES
0	54	41	63	29
1	53	54	58	19
2	60	51	44	25
3	51	59	18	23
4	57	60	12	20
5	‡	65	4	16
6	‡	69	2	6
7-9	‡	73	1	25

*The difference between the proportion of questions answered correctly by those whose associates had had none of the diseases and by those whose associates had had 7 or more of the diseases is significant at the 0.05 level.

†Twelve respondents gave incomplete answers about their own diseases and 51 about their associates' diseases. These cases are not shown in the Table.

‡Fewer than 5 cases.

TABLE V. LEVEL OF INFORMATION ABOUT DISEASE BY EDUCATION LEVEL

	AVERAGE PER CENT OF QUESTIONS ANSWERED CORRECTLY:*			
	HIGH SCHOOL GRADUATE OR ABOVE (76 CASES)	1-3 YEARS HIGH SCHOOL (38 CASES)	PRIMARY SCHOOL GRADUATES (47 CASES)	7 YEARS OR LESS (34 CASES)
Total information	67	55	51	37
Tuberculosis	85	80	69	55
Stroke	65	55	50	28
Stomach ulcer	52	50	38	39
Syphilis	80	72	51	44
Diabetes	83	73	70	50
Coronary thrombosis	48	37	37	22
Arthritis	66	58	55	46
Asthma	63	50	48	35
Change of life	71	45	49	30
Leukemia	54	38	36	18
Etiology	68	55	47	31
Treatment	66	59	56	43
Symptoms	62	52	48	34

*The difference between the per cent of all questions answered correctly by the high school graduates and by those with fewer than 8 years of schooling is significant at the 0.01 level.

school graduates answered two-thirds of the questions correctly while respondents who had not completed grade school made errors on two-thirds of the questions. Education appeared to have the greatest influence on information about menopause, stroke, syphilis, and leukemia. Significant differences also appeared in knowledge of diabetes, tuberculosis, and asthma. The outstanding gaps in the low-level groups were in leukemia, coronary thrombosis, stroke, menopause, and asthma.

5. *Patient's Knowledge in Relation to Age.*—For the age group under 30 years, 52 per cent of the questions were answered correctly. For the group aged 30 to 49, 62 per cent were correct; and in people over 50 years, 51 per cent were correct. The differences among these groups are not statistically significant, indicating that age alone is not a factor in the level of information.

6. *Patient's Knowledge in Relation to Being Native or Foreign Born.*—The striking finding here is that with comparable education no significant differences could be demonstrated in the information levels of native and foreign-born persons (Table VI).

VOL. 6 1957

TABLE VI. LEVEL OF INFORMATION ABOUT DISEASE AMONG THE NATIVE AND FOREIGN-BORN, CROSS-CLASSIFIED BY EDUCATION LEVEL

EDUCATION LEVEL	CORRECT ANSWERS BY NATIVITY			
	NATIVE		FOREIGN-BORN	
	CASES	PER CENT	CASES	PER CENT
High school graduates	59	71	16	70
1-3 years high school	29	59	8	70
Eighth grade	34	56	13	51
7 years or less	15	42	18	42

7. *Patient's Knowledge in Relation to Sex.*—Women correctly answered 58 per cent of all the questions as compared to 51 per cent for the men. This difference is not statistically significant for all test questions combined (Table VII).

DISCUSSION

This study constitutes a step in an attempt to improve patient-physician communication. Obviously the nature of the disease in any given case will modify what the doctor will wish to tell his patient, particularly when the disorder is chronic or fatal. This problem has been amply discussed in a number of publications.[3,4] Even in such conditions, however, the following questions come to mind: (1) What level and type of information should the patient have? (2) What is the most effective technique for imparting this information? The answer to the first question will most likely remain a topic of discussion by physicians as long as medicine is practiced, but the second is subject to experimental testing. Our data provide the jumping-off place for such a project by offering a guide to the

average person's knowledge. Admittedly the study suffers from certain defects. The sample is drawn from people who are seeking medical advice. Since patients are our chief concern, however, this is not a serious objection. The group is deficient in persons with more than a high-school education. For college graduates, one might expect better scores, although there is no reason to believe that the trends would be significantly different.

Certain specific points brought out by the data are worth noting. The group knew more about diseases in which there have been intensive education programs (i.e., tuberculosis, diabetes, and syphilis) than about those less extensively publicized. The poor showing in the case of coronary thrombosis (38 per cent correct answers) is striking when one considers that of all the potentially fatal disorders studied, it has the highest mortality rate* (see tabular material in footnote). It may be that patients know more about other diseases because they are longer lasting and therefore provide more opportunity for acquiring knowledge.

TABLE VII. LEVEL OF INFORMATION ABOUT DISEASES BY SEX*

INFORMATION AREA	AVERAGE PER CENT OF CORRECT ANSWERS	
	MEN	WOMEN
Total information	51	58
Tuberculosis	67	77
Stroke	47	54
Stomach ulcer	43	46
Syphilis	64	64
Diabetes	63	75
Coronary thrombosis	37	39
Arthritis	59	56
Asthma	43	55
Change of life	44	57
Leukemia	34	45
Etiology	49	54
Treatment	52	60
Symptoms	47	53
Number of cases	69	145

*The difference between the proportion of questions answered correctly by men and by women are significant at the 0.10 level for diabetes, asthma, and change of life.

DISEASE	ANNUAL DEATH RATES PER 100,000 POLICY HOLDERS, 1955[5]
Tuberculosis	8.1
Diabetes	14.9
Syphilis	2.2
Stroke (C.V.A.)	64.9
Stomach ulcer	4.7
Leukemia	4.2
Coronary thrombosis	108.2

*An interesting study by Bertrand and Storla demonstrates the surprising inadequacy of lay knowledge about heart disease as a whole.[6]

A number of interesting misconceptions about illness appeared among the answers. For example, 60 per cent of the respondents believed that the chief disturbance in leukemia is that "the white cells destroy the red cells." Forty-four per cent believed that stomach ulcer produces abdominal pain immediately after eating. Twenty-five per cent thought that in stomach ulcer there is a small growth in the stomach cavity. This points to the possibility of confusion with cancer and suggests a source of anxiety when the diagnosis of ulcer is entertained or established. Thirty-three per cent thought the commonest symptom of coronary thrombosis was a sharp shooting pain in the chest, while only 20 per cent favored the more accurate description. The clinical implications are obvious. Other misconceptions in smaller segments of the group were that in the early stages, syphilis may produce severe pain on urination (27 per cent)—apparently a confusion between syphilis and gonorrhea; the diabetic in many cases has swollen joints (15 per cent); and change of life usually causes permanent emotional upsets and loss of interest (17 per cent).

It is clear from the foregoing that persons in the study group were poorly and irregularly informed about disease. They knew roughly as much about treatment (58 per cent correct replies) as about symptoms (51 per cent correct) and etiology (53 per cent). Since symptoms are what send the patient to the doctor while decisions about treatment are chiefly the doctor's responsibility, educational efforts aimed at increasing knowledge of the meaning of symptoms seem well worth while.

Perhaps the most surprising finding of all is that having one or more diseases does not substantially increase the patient's information about these conditions in comparison with those who remain free of them. The reasons are not clear. It may be that the patient unconsciously rejects explanations of his disease. Other possible reasons are that physicians fail to explain illness adequately because they feel the patient is best kept uninformed, because they feel it unnecessary, or because of real or fancied limitations of time.

The superior knowledge of respondents whose associates had tuberculosis, arthritis, menopause, asthma, or stroke suggests that friends or family get better information than the patient. In certain situations this probably results from the physician's talking with greater frankness to associates than to the patient.

The tendency for higher levels of education to be associated with superior knowledge of disease was to be anticipated. Yet even high school graduates are poorly informed about coronary thrombosis, stomach ulcer, and leukemia.

SUMMARY AND CONCLUSIONS

The level of information about ten common diseases of 214 randomly selected clinic patients was tested by means of a multiple choice self-administered questionnaire. This is the first step in a study to devise new techniques for doctor-patient communication.

The respondents answered only 55 per cent of the questions correctly. They were best informed about diseases which have been highly publicized (tuberculosis, diabetes, and syphilis). Knowledge about coronary thrombosis was particularly meager (only 38 per cent answering correctly) despite its high incidence.

Information tended to improve with level of education, independent of the individual's country of origin.

Patients who had suffered from one or more diseases were no better informed than the rest of the group. However, those whose associates had been ill had significantly more information than the group as a whole in the case of tuberculosis, arthritis, menopause, asthma, and stroke.

It is apparent that knowledge about disease in the group studied is spotty and inadequate for optimal patient-physician cooperation in the management of these illnesses. Patients' lack of information should be taken into account in planning for their care, and ways must be devised for educating them to a better level of understanding.

We wish to express our thanks to Dr. George G. Reader, Director of the Comprehensive Care and Teaching Program at Cornell University Medical College for encouragement and valuable suggestions in connection with this study.

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5
957

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APPENDIX

DO NOT SIGN

Medical Clinic Questionnaire

We are trying to make it easier for doctors to explain clearly to patients some of their medical problems. It would help us if, while you are waiting to be seen, you would go through this questionnaire and indicate what each of the underlined terms means to you.

DIRECTIONS: Each condition listed below is followed by three statements. Some statements are partly true, but only one statement is entirely correct. Circle the number in front of the one statement which seems entirely correct to you. If you know nothing about the condition, circle ④ Don't know. Disregard the bracketed numbers on the left side of the page.

Tuberculosis of the lungs is due to:

(4)
1. Prolonged exposure to the cold
2. Infection with a germ
3. Anemia and vitamin deficiency
4. Don't know

The commonest symptoms of TB of the lungs are:

(5)
1. Pain in the chest after exercise
2. Chronic cough and sputum
3. Wheezing sounds on deep breathing
4. Don't know

Many patients with TB of the lungs are now successfully treated by:

(6)
1. Vitamin injections and special diets
2. Prolonged exposure to the sun and special exercises
3. Antibiotics and bed rest
4. Don't know

TB of the lungs is best diagnosed by:

(7)
1. Chest x-ray
2. Observing temperature and weight
3. Stethoscope examination of the chest
4. Don't know

A stroke is:

(8)
1. A blood clot to the heart
2. Blood clot in the arms or legs causing paralysis
3. Hemorrhage or blood clot in the brain
4. Don't know

Most common symptoms of a stroke are:

(9)
1. Severe chest pain spreading to the arm
2. Paralysis and unconsciousness
3. Rapid and irregular heartbeat
4. Don't know

After a stroke a patient:

(10)
1. Is usually helped by antibiotics
2. Often improves with time
3. Rarely regains the power of speech
4. Don't know

Persons with stomach ulcer often:

(11)
1. Have severe cramps and diarrhea
2. Have pain in the abdomen right after eating
3. Have pain in the abdomen which is relieved by eating
4. Don't know

Treatment for ulcer tries to:

(12)
1. Correct bowel disturbances
2. Speed up digestion
3. Cut down on acid stomach juices
4. Don't know

Stomach ulcer is a condition in which:

(13)
1. There is a small growth in the stomach cavity
2. There is a tightening and thickening of the stomach muscles
3. A portion of the stomach lining has been eaten away
4. Don't know

Syphilis is caused by:

(14)
1. A germ from a syphilitic person
2. Lack of cleanliness
3. Excessive sexual activity
4. Don't know

Syphilis is most successfully treated with:

(15)
1. Sunshine and fresh air
2. Penicillin
3. High protein diet
4. Don't know

Syphilis is a disease that:

(16)
1. Clears up in several weeks with rest and good nutrition
2. Almost always leads to blindness and insanity
3. Can usually be cured if treated early
4. Don't know

In the early stages syphilis may produce:

(17)
1. Severe burning on urination
2. Such mild symptoms as to be almost unnoticed by the patient

VOL 6 195

3. Marked decrease in appetite
4. Don't know

In treating diabetes the patient usually has to limit in his diet:

(18)
1. Salt
2. Sugar
3. Coffee
4. Don't know

Diabetes is usually diagnosed by examining the:

(19)
1. Urine
2. Blood pressure
3. Bowel movement
4. Don't know

Diabetes is a disease in which the following medicine is often prescribed:

(20)
1. Penicillin
2. Digitalis
3. Insulin
4. Don't know

OL.
6
957

The chief disturbance in diabetes is:

(21)
1. The inability of the body to make good use of certain foods
2. Failure of the body to manufacture enough blood cells
3. Failure of the intestines to retain certain foods
4. Don't know

The diabetic person in many cases:

(22)
1. Has pain in his chest
2. Has swollen joints
3. Gets infections easily
4. Don't know

The commonest symptom of coronary thrombosis is:

(23)
1. Sharp shooting pain in the chest
2. Paralysis
3. Steady pressing pain in the chest
4. Don't know

Coronary thrombosis is:

(24)
1. An attack of rapid irregular heartbeat
2. The same as a stroke
3. A blood clot in a heart artery
4. Don't know

Usual treatment for coronary thrombosis is:

(25)
1. Several weeks bed rest
2. Surgery
3. Penicillin or aureomycin injections
4. Don't know

Coronary thrombosis:

(26)
1. Is almost always fatal
2. Is often followed by recovery
3. Is not serious for those over 50
4. Don't know

Arthritis is a condition in which:

(27)
1. The joints are painful, swollen or misshapen
2. The joints usually become completely stiff and u[illegible]es
3. There are imaginary joint pains caused by nervousness
4. Don't know

Arthritis is:

(28)
1. Often improved by treatment
2. A condition which cannot be helped by treatment
3. Is now usually cured by antibiotics
4. Don't know

In the commonest types of arthritis the cause is:

(29)
1. A vitamin deficiency
2. Chronic infection
3. Unknown
4. Don't know

Asthma is a condition in which there is:

(30)
1. A severe chest cold
2. Wheezing and difficulty in breathing
3. A form of pneumonia
4. Don't know

Treatment in asthma:

(31)
1. Is rarely successful
2. Usually helps the patient somewhat
3. Usually requires change of climate
4. Don't know

An asthmatic attack can be brought on by:

(32)
1. An emotional disturbance
2. Coming in contact with a person with the disease
3. Excess stomach acid
4. Don't know

Change of life:

(33)
1. Usually causes permanent emotional upsets and loss of interest
2. Often passes with little disturbance
3. Usually produces weakness, indigestion and constipation
4. Don't know

The change of life period can be:

(34)
1. Treated if necessary by pills or injections
2. Cannot be helped except by time
3. Often must be treated by prolonged bed rest
4. Don't know

Change of life is due to:

(35)
1. Normal decrease in the activity of certain glands
2. Increased tension associated with advancing age
3. Gland disturbances resulting from child-bearing
4. Don't know

Leukemia is:

(36)
1. A cancerlike condition
2. A severe infection
3. A condition resulting from iron deficiency
4. Don't know

In leukemia, the chief disturbance is that:

(37)
1. The white cells become very numerous
2. The white cells destroy the red cells
3. The bones become very brittle
4. Don't know

Treatment of leukemia:

(38)
1. May cure it
2. May slow it up

3. Has no effect
4. Don't know

Patients with leukemia usually have at some time:

(39)
1. Pain in the upper abdomen after eating
2. Marked constipation and nausea
3. Fatigue and paleness
4. Don't know

	Have you ever had any of the following conditions yourself? (Check √ "yes" or "no")	Have you ever known anyone who has had any of the following conditions? (Indicate whether the person was your wife, brother, friend, work associate, etc. (Check √ "yes" or "no")
Tuberculosis	(40) Yes_____1 No_____2	(50) Yes_____Who?_____ No_____2
Stroke	(41) Yes_____1 No_____2	(51) Yes_____Who?_____ No_____2
Syphilis	(42) Yes_____1 No_____2	(52) Yes_____Who?_____ No_____2
Diabetes	(43) Yes_____1 No_____2	(53) Yes_____Who?_____ No_____2
Coronary Thrombosis	(44) Yes_____1 No_____2	(54) Yes_____Who?_____ No_____2
Arthritis	(45) Yes_____1 No_____2	(55) Yes_____Who?_____ No_____2
Asthma	(46) Yes_____1 No_____2	(56) Yes_____Who?_____ No_____2
Anemia	(47) Yes_____1 No_____2	(57) Yes_____Who?_____ No_____2
Change of Life	(48) Yes_____1 No_____2	(58) Yes_____Who?_____ No_____2
Leukemia	(49) Yes_____1 No_____2	(59) Yes_____Who?_____ No_____2

(60) How old are you? _____years.
(61) Sex: Male_____1 Female_____2
(62) In what country were you born? _____
If born *outside* United States, how many years have you lived in the United States? _____
Highest grade completed in school (circle one number):
(63) 1 2 3 4 5 6 7 8 9 10 11 12

VOL.
6
1957

Special Article

PHEOCHROMOCYTOMA: A REVIEW OF THE LITERATURE

DALE B. WATKINS, COMMANDER (MC) USN

PHILADELPHIA, PA.

From the U. S. Naval Hospital, Philadelphia, Pa.

(Received for publication March 4, 1957.)

HISTORY

PHEOCHROMOCYTOMAS are functionally active tumors of sympathetic nerve cells, occurring most commonly in the adrenal medulla. The first report of the associated clinical syndrome was that of Fraenkel[1] in 1886. In the following year von Neusser[2] reported certain cases of hypertension which were associated with tumor of the adrenal gland. The first description of pheochromocytomas was made by Manasse[3] in 1893, and later the chromaffin system from which these tumors arise was described by Kohn.[4] In 1913, Helly[5] reported a case with hypertension and glycosuria. The paroxysmal symptoms which are manifested by the tumor because of the release of pressor substance were first described, in 1922, by Labbé, Tinel, and Doumer.[6] In 1927, C. H. Mayo[7] removed an epinephrine-secreting tumor from a patient with hypertension, with subsequent return of the blood pressure to normal. Pincoffs,[8] in 1929, made the first preoperative diagnosis of a pheochromocytoma in a patient with paroxysmal hypertension. This was later successfully excised. Coincidentally, Rabin[9] had determined that the amount of epinephrine in a pheochromocytoma was in excess of that found in the adrenal medulla and associated this with the clinical syndrome present. Beer, King, and Prinzmetal,[10] in 1937, demonstrated the presence of a pressor agent thought to be epinephrine in a patient with pheochromocytoma. The first provocative test of pheochromocytoma using histamine was described by Roth and Kvale,[11] in 1945.

Although the pharmacologic properties of norepinephrine were described by Barger and Dale,[12] in 1910, its presence in tissues was not demonstrated until 1946, when von Euler[13] isolated it from adrenergic nerve fibers. Evidence that the adrenal medulla contains norepinephrine, as well as epinephrine, was first advanced by Holtz, Credner, and Kroneberg,[14] in 1947. Two years later, the presence of epinephrine and norepinephrine in pheochromocytomas was independently reported by Holton,[15] and by Goldenberg and his associates.[16] Tullar,[17] in 1949, reported the separation of *l*-arterenol from natural U.S.P. epinephrine.

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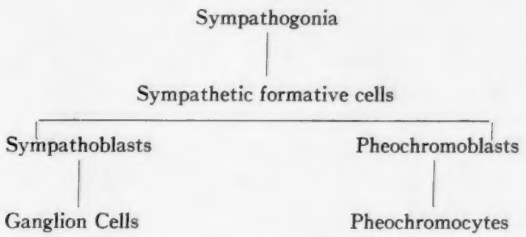
VOL.
6
1957

DEVELOPMENT

The development of the sympathetic nervous system has been reviewed by Hollingsworth[18] who describes the derivation of ganglion cells from the neural crest by a process of maturation and differentiation. These cells are thus ectodermal in origin. The undifferentiated cells move to the dorsal surface of the sympathetic ganglion and form rounded masses in depressions of the ganglia. For this reason, they have been called paraganglion cells. These undifferentiated cells also give rise to the essential cells of the adrenal medulla and, in maturity, produce epinephrine and norepinephrine. Other paraganglionic cells are connected with the parasympathetic system and are found in the carotid body, the cardioaortic body,[19] and along the course of the vagus and the glossopharyngeal nerve and its branches in the middle ear.[20] Several masses of the cells have been described in the heart, testes, liver, and kidneys, although aberrant chromaffin tissue may be present elsewhere. Epinephrine-secreting cells may also be found in the sympathetic plexuses adjacent to the aorta, particularly in the region of the inferior mesenteric artery. These cells were first described by Zuckerkandl and bear his name. Hormone-producing tumors (pheochromocytomas) usually occur in the abdominal or thoracic cavity, other paraganglionic cells of the sympathetic as well as the parasympathetic system being normally inert. For this reason, Stout[21] has recommended that the term paraganglioma be confined to functionally inactive tumors.

Rabin[9] schematically represents the maturation of the sympathetic nervous system and pheochromocytes as follows:



McCullagh and Engel[22] have classified tumors of the adrenal medulla into three types: (1) sympathoblastomas arising from immature sympathoblasts; (2) ganglioneuromas from mature ganglion cells; and (3) pheochromocytomas from mature chromaffin cells, or pheochromoblasts.

Tumors of the adrenal medulla are usually classified according to the preponderant cell type, although sympathogoniomas and sympathicoblastomas are often grouped as neuroblastomas. Stout[21] has found that pheochromocytomas and pheochromoblastomas cannot always be classified separately inasmuch as both types of cells are usually included.

In a review of the literature up to 1948, Brines and Jennings[23] had assembled about 210 authenticated cases of tumors of the sympathetic nervous system.

The development of the dark brown stain by epinephrine in suprarenal medullary tissue has been ascribed to its reaction with chromic acid or potassium

dichromate (Henle[24]) and has led to acceptance of the term "chromaffin reaction." This designation is erroneous, however, as the process is solely one of oxidation. The color change of epinephrine can be incited by oxidizing agents other than chromium compounds.

PATHOLOGY

The tumors reported have varied in weight from 5 Gm. to more than 2,000 Gm., and in size from 1 to 12 cm. in diameter.[25] They are usually encapsulated, of a reddish-brown to yellow color, and are spherical or oval in shape. They may be hemorrhagic, necrotic, or cystic. Usually, the remnants of the suprarenal cortex can be observed on the surface of the tumor. The tumors are made up of nests or cords of cells, usually polyhedral in shape, which are separated by a delicate connective tissue stroma that is often vascular. There is strong resemblance of the cells to the suprarenal medulla though cortical and neural elements may be present.[26] The nuclei are large, vesicular, irregular in size and shape, and the nucleoli are often prominent. The cells vary in size, but the cytoplasm is abundant and often contains fine granules. The identification may be difficult because of an atypical histologic or polymorphic appearance, the cells often being fusiform and spindle-shaped, with much variation in size. The cytoplasm may be diminished and may not contain granules. Melanin may be observed. The nuclei may be small, pyknotic, and devoid of nucleoli. Mitoses are seen occasionally, though they may not be observed in tumors which have known metastases.

Karsner[27] believes that approximately 8 per cent of paragangliomata are malignant. In McGavack's[26] series, all had metastases to the regional lymph nodes. The following metastatic sites were also observed: thoracic lymph nodes, 5; liver, 4; bones, 3; lungs, 3; pleura, 2; skin, 2; intestines, 1; kidney, 1. Cross and Pace[28] have reported a patient with malignant pheochromocytoma and paroxysmal hypertension with metastases to the cervical spine.

Multiple-functioning metastases from a malignant pheochromocytoma and the therapeutic problems entailed have been discussed by Brennan and Allen,[29] who found Dibenzyline to be the most effective adrenergic-blocking agent in the control of prolonged hyperepinephrinemia.

INCIDENCE

Pheochromocytomas are relatively rare tumors although over 300 cases have now been reported.[30] Kvale and Roth[31] reported the incidence of pheochromocytoma to be 2 per cent of 900 patients studied because of hypertension or "various types of attacks." Aranow[32] quotes Smithwick, who, in describing bilateral lumbodorsal splanchnicectomy in 1,700 patients with intractable hypertension, stated that 0.47 per cent had pheochromocytomas discovered on examination of the adrenals. Pheochromocytoma had been diagnosed in three others prior to surgery. Hyman and Mencher,[33] Calkins and Howard,[34] and Colston[35] have reported pheochromocytoma in two members of a family, and Roth and her associates[36] have reported it in 3 siblings with bilateral tumors. They appear in equal frequency[25] in both men and women, and usually between the

ages of 20 and 50. Fingerland[37] and Berkheiser and Rappaport[38] have each reported a tumor in a 71-year-old man, and a pheochromocytoma in an 81-year-old woman has been reported by Ortega.[25] When the tumor is present in infants or very young children, it is usually atypical and may be multiple, and as such tumors excrete norepinephrine predominantly little metabolic disturbance occurs. Lindl[39] has reported one in an infant 5 months old. Neff and co-workers[40] have described a 1-year-old infant with pheochromocytoma, hirsutism, precocious development of the genital organs, and obesity.

The suprarenal glands are the site of origin of the neoplasm in about 90 per cent of the cases, with a predilection of the tumor for the right adrenal gland. Sixteen per cent of those reported have been bilateral or multicentric.[36,41] Several have been intrathoracic.[42-43b] One was recently reported in a patient in whom the only clue to localization of the tumor was the fact that symptoms could be provoked on deep palpation of the epigastrium. The tumor was ultimately found under the liver behind the inferior vena cava after nine negative surgical explorations.[44]

In a review of the 165 cases reported prior to 1944, MacKeith[45] found concomitant neurofibromatosis in 9 patients. Others have recently been reported by Davis, Hull, and Vardell,[46] Minno, Bennett, and Kvale,[47] Glushien, Mansuy, and Littman,[48] and Mandeville.[49]

PATHOLOGIC PHYSIOLOGY

The presence of pressor substances in the blood during hypertensive crises was first demonstrated by Beer, King, and Prinzmetal.[10] They removed 200 c.c. of blood from the antecubital vein of a patient during an attack and compared the pressor effect with that of the blood of a control subject, as determined by a modification of the Pissemski method of perfusion of the denervated rabbit's ear. This work was repeated by Hyman and Mencher.[33] That norepinephrine might be a chemical effector at certain adrenergic neuroeffector junctions had been suggested in 1938,[50] though many years elapsed before pressor substances were studied exhaustively by Goldenberg and his colleagues.[51,52] They infused epinephrine intravenously and, by catheterizing the right side of the heart, demonstrated an increase in cardiac output as determined by the direct Fick principle. They concluded that the increase in blood pressure following epinephrine injection occurred because the rise in the cardiac output exceeded the over-all vasodilatation. They also found that the vasodilatation in the vascular bed of the muscles exceeds the total vasoconstriction in the skin, mucous membranes, and splanchnic area. Infusions of epinephrine were observed to increase the heart rate, the metabolic rate, the rate of glycogenolysis, and the sudorific action of the sweat glands. They found that norepinephrine, on the other hand, caused little change in cardiac output, but precipitated a rise in over-all peripheral resistance, creating an elevation of the systolic and diastolic blood pressures. Significantly, the patients had no subjective awareness of this. The increase in the metabolic rate was less marked, and the pulse rates were lower than those of epinephrine-infused cases. Likewise, glycogenolysis was of a lower order.

The cardiovascular actions of the norephinephrine, when simultaneously infused with epinephrine, were found to be antagonistic rather than synergistic or additive, and the expected increase in cardiac output did not occur.

In a recent review of the fundamental functional differences between the two drugs, Sokoloff, King, and Wechsler[53] have presented Tables I and II.

TABLE I. CARDIOVASCULAR AND METABOLIC EFFECTS OF INTRAVENOUS INFUSIONS OF *l*-NOREPINEPHRINE AND EPINEPHRINE IN NORMAL MAN

	l-NOREPINEPHRINE	EPINEPHRINE
Systolic blood pressure	+++	+++
Diastolic blood pressure	++	♂
Mean blood pressure	++	+
Pulse rate	−	++
Cardiac output	♀	+++
Direct action on heart	0	++
Total peripheral vascular resistance	+++	♀ −
Pulmonary arterial blood pressure	+	+
Total body oxygen consumption	0	++
Cerebral oxygen consumption	0	++
Blood sugar	♂	+++
Activation of pituitary-adrenal axis	0	++

+ indicates increase; − indicates decrease; 0 indicates no change; number of + or − indicates degree; ♂ indicates slight increase, if any; ♀ indicates slight decrease, if any.

TABLE II. EFFECTS OF INTRAVENOUS INFUSIONS OF *l*-NOREPINEPHRINE AND EPINEPHRINE ON VARIOUS VASCULAR BEDS IN NORMAL MAN

REGION	FUNCTION	*l*-NOREPINEPHRINE	EPINEPHRINE
Coronary	Blood flow	++ ?	+ ?
	Vascular resistance	−− ?	− ?
Cerebral	Blood flow	−	+
	Vascular resistance	++	0
Splanchnic	Blood flow	−	+
	Vascular resistance	++	−
Skeletal Muscle	Blood flow	0 or −	++
	Vascular resistance	+	−
Renal	Blood flow	−−	−−
	Vascular resistance	+++	+++
Skin	Blood flow	−	−−
	Vascular resistance	++	+++

+ indicates increase; − indicates decrease; 0 indicates no change; the number of + or − signs indicates degree.

They state: "Considerable chemical and pharmacological evidence exists to indicate that *l*-norepinephrine is a natural chemical mediator of sympathetic adrenergic nerve action, and it is probably identical with 'Sympathin E,' the

postulated excitatory chemical mediator of the sympathetic nervous system of Cannon and Rosenblueth. It may well be, as von Euler suggests, that in the body *l*-norepinephrine is a mediator of general sympathetic functions while epinephrine is reserved for more specialized effects, probably metabolic in nature. The difference in action following a systemic administration may simply reflect the different functions within the body." According to Blaschko and his associates,[54] there is considerable evidence to suggest that norepinephrine may be a precursor to epinephrine.

A normal adrenal gland contains about 1.0 mg. of pressor substances per gram though the content in tumors may be twenty times this figure (Belt and Powell[55]). Aranow[32] analyzed five pheochromocytomas, using techniques which permit the separate determination of the two hormones, and found the percentage of norepinephrine to vary from 50 to 90. It is the simultaneous secretion of varying proportions of these principles which produce the wide range of clinical phenomena. The only evidence of the presence of a neoplasm which secretes a high percentage of norepinephrine may be high blood pressure, and this may be intermittent or continuous. When increasing amounts of epinephrine are released into the circulation, the symptoms of the tumor are manifest. The physiologic manifestations of the pressor substances in pheochromocytomas have also been reviewed by Pitcairn and Youmans[56] and Beyer and colleagues.[57]

OL.
6
957

SYMPTOMS

Patients in whom pheochromocytomas have been demonstrated usually have had a history of characteristic attacks with one or more of the symptoms which make up the adrenal-sympathetic syndrome (Aranow[32]). He[58] has described the following classification: (1) symptom-free individuals in whom the tumor is discovered as an accidental or incidental finding, such as at operative exploration, by radiography, or at autopsy; (2) symptom-free individuals, whose death after some slight trauma such as a minor operative procedure may lead to discovery at autopsy; (3) the patients who present the "adrenal sympathetic syndrome" with signs and symptoms of excess epinephrine or norepinephrine in the body; and (4) patients in whom continuous hypertension cannot be distinguished clinically from essential or malignant hypertension.

DeCourcy and DeCourcy[30] feel that the following conditions indicate an increased probability of the tumor:

> (1) Patients with sustained or intermittent hypertension, with or without a history of vasomotor attacks or paroxysms, who have as associated manifestations: hypermetabolism, diabetes mellitus, precordial pain (perhaps misdiagnosed as angina pectoris), tachycardia, palpitation.
>
> (2) Patients with wide fluctuations of blood pressure, often in the normotensive range.
>
> (3) Refractory "hyperthyroidism" with hypertension.
>
> (4) Normotensive patients who manifest paroxysmal episodes of hypertension, or who have a history of "attacks" or "spells" whether known to be hypertensive or not, these attacks being accompanied by: headache, palpitation, tachycardia or bradycardia, precordial or abdominal pain, pallor, flushing, nausea, vomiting, evidences of vasoconstriction in the extremities, and profuse sweating.
>
> (5) Hypertension in children and young adults.

(6) Hypertension in the early months of pregnancy or hypertensive crisis during delivery or postpartum.

(7) Sudden loss of vision, or other ocular disturbances in a normotensive individual or one with moderate hypertension.

(8) Hypertensive crisis after minor trauma, an injection, or a diagnostic procedure.

(9) Hypertensive crisis during anesthesia or surgery.

(10) Hypertension persisting after removal of one pheochromocytoma.

The signs and symptoms which manifest the presence of the tumor may be progressively severe and more frequent over a period of several weeks to many years. There may be palpitation, anxiety, precordial distress, a sensation of numbness or constriction of the extremities, a feeling of fullness in the neck or throbbing in the head, blurred vision, dilatation of the pupils, breathlessness, sweating, headache,[59] restlessness, pain in the flanks, abdomen,[60] or extremities, epigastric distress, colic, nausea, vomiting, vertigo, tremor, prostration, or semiconsciousness, and cerebral vascular accidents may occur.[61-63] There may be urinary frequency or nocturia, though rarely urinary suppression, and elevation of the blood urea nitrogen may occur. The attacks are usually quite rapid in onset with a gradual disappearance of symptoms. They may be of several minutes to many hours in duration. Most often they occur at night or early in the morning. They may be incited by emotion, changes in posture, or pressure upon the tumor site, a heavy meal, physical effort, prolonged fasting, gargling, shaving, sneezing, urinating, trauma, or situations which cause a fall in blood pressure. Following an attack, there is usually a period of fatigue, though prolongation may lead to shock or death,[62a] possibly because acute hyperepinephrinemia is followed by marked glucose mobilization and gross potassium transfer. There is often an initial flush, which is followed by circumoral pallor or pallor of the extremities, or other peripheral vascular phenomena. Cyanosis, pilomotor activity, profuse diaphoresis, hypertension, and tachycardia have been reported. Bradycardia may be observed, however. There may be marked elevation of body temperature and leukocytosis.

Prolonged hypertension may lead to the characteristic vascular changes of the retina,[64] cerebrum, heart, or kidneys.[65,66] Cardiac dilatation or hypertrophy and pulmonary edema may supervene. Green reported that there was definite cardiac enlargement in 17 of 24 patients, and that the weight of the heart was above average or in the outer limits of normal in three others. The electrocardiographic changes have been recorded in detail by MacKeith.[45]

An abdominal mass may be palpated which may be an organ displaced by the mass rather than the tumor itself. Renal displacement by the tumors may be demonstrated by intravenous or retrograde urography. If these examinations fail to delineate the tumor site, extraperitoneal pneumography may be utilized in selected cases.[13,67,68]

Pigmentation of the skin may be seen when the tumor is associated with neurofibromatosis.[46-49]

Mortell and Whittle[69] reported a patient who developed convulsive seizures at the age of 28. These occurred at intervals for 20 years and ceased following removal of a pheochromocytoma.

Paroxysms of hypertension with or without convulsions have also been described in eclampsia, angina pectoris, brain[70] and cord[71] injury (traumatic, vascular, inflammatory), hysteria, meningitis, migraine, neuroses, periarteritis nodosa, psychoneuroses, sciatic neuritis, thyrotoxicosis ("thyroid crisis"), vagus nerve affections, lead poisoning, renal disorders, aortitis, infectious diseases, and diseases of the central nervous system, including tabes and brain tumor. Similar findings may be observed in the anxiety states, and psychiatric evaluation is frequently indicated.[72] Involvement of the autonomic centers of the hypothalamus by an encapsulated tumor which led to autonomic, diencephalic epilepsy with symptoms suggesting pheochromocytoma, has been reported by Penfield,[73] and the syndrome in a 17-year-old boy has been reported by Geoghegan and Mueller.[74]

VOL.
6
1957

ENDOCRINOLOGIC DISTURBANCES

Diabetes in the presence of pheochromocytoma has been reported.[75-77] It usually disappears after removal of the tumor. Elevated fasting blood sugar levels are common in these patients, as are abnormal glucose tolerance curves. These tendencies may be constant, or may occur only during paroxysms of hypertension, and, if so, may be attended by glycosuria. Hyperplasia of pancreatic tissue has been reported as an autopsy finding in one case.[78] Altered function of the adrenal cortex has been suggested by reports of disturbances in the blood levels of chloride, potassium, and low urinary ketosteroids. There have been many reports of elevation of basal metabolic rates.[79] Some patients have been shown to have hyperthyroidism, and paroxysmal swelling of the thyroid has been seen during attacks.[80] Epinephrine may stimulate the thyroid either directly or through the mediation of the pituitary, according to Raab.[81] He has shown that thyroxin potentiates the normal and toxic effects of epinephrine. The adrenogenital syndrome in a 1-year-old infant has been previously mentioned.[40] The presence of acromegaly associated with pheochromocytoma has also been reported.[82]

The patient with pheochromocytoma will follow the course which characterizes his response to the abnormal physiologic disturbances evoked. If the disease is not recognized, death may occur during a paroxysm. Chronic disease may be characterized by a fixed systolic and diastolic blood pressure with secondary changes in the cardiovascular system. Since these changes and the metabolic and endocrinologic disturbances which they produce are usually reversible, removal of the tumor may be expected to ameliorate their effects. Recent observations have demonstrated that protracted disease may lead to a self-perpetuating mechanism and that removal of the pheochromocytoma may not necessarily insure homeostasis. The studies of Peart[82a] indicate that temporization is to be avoided.

PHARMACOLOGIC TESTS FOR PHEOCHROMOCYTOMA[83]

Pharmacologic tests used in the diagnosis of pheochromocytoma are divided into those causing pressor or depressor responses. Of drugs inducing release

of pressor substances such as histamine, tetraethylammonium bromide, and Mecholyl, histamine is the most useful. All may induce a paroxysm which can be as severe as a spontaneous episode.

HISTAMINE

Though the mechanism of action of histamine has not been fully elucidated, evidence has been presented to support the view that it liberates epinephrine by stimulating the adrenal medulla directly and not by a reflex response.[84] The test is used in patients in whom the resting blood pressure does not exceed 150/110 and is always preceded by a cold pressor test to establish comparative responses for the two procedures. Roth and Kvale,[11] who introduced the test in 1945, report that barbiturates and other sedatives have an inhibitory action on the cold pressor test, but not on the histamine test, and warn that comparison following sedation might lead to misleading results. The patient rests in a quiet room for a period of half an hour in order to establish a base line blood pressure, which is determined at one-minute intervals for a period of 5 minutes. Five per cent glucose in water is introduced intravenously, and blood pressure determinations are recorded until the blood pressure is stabilized. Then 0.025 to 0.05 mg. of histamine is rapidly introduced via a three-way stopcock attached to the intravenous infusion, and the blood pressure is recorded at one-minute intervals for 15 minutes.

If the systolic blood pressure rises 60 mm. of mercury or more and the diastolic pressure rises 30 mm. or more within 1 to 4 minutes after the injection, with return to the preinjection blood pressure after 5 to fifteen minutes or longer, the test is considered positive provided the elevation exceeds the cold pressor response.

In a recent review of tests used in pheochromocytoma, Chapman and Singh[84] state that they can find only two instances in which a proved false positive histamine test occurred, one of which was their own.

Inasmuch as maximum pressor responses have been recorded, it is advisable to have 15 to 20 mg. of benzodioxane or Regitine at hand for intravenous administration if necessary.

TETRAETHYLAMMONIUM BROMIDE

In 1947, La Due, Murison, and Pack[85] reported the intravenous injection of 0.4 Gm. of tetraethylammonium bromide as a diagnostic test for pheochromocytoma. A paroxysmal increase in blood pressure was induced which persisted for 15 minutes. This was in contrast to the return to normal in 5 minutes following the injection of histamine. The degree of rise in blood pressure could be controlled by allowing the patient to sit up or stand, and the use of a tilting bed or table for the performance of the test was advised. Because of its unreliability, this drug, as well as tetraethylammonium chloride, has been found to be of less value than histamine.

MECHOLYL

Acetyl-beta-methylcholine (Mecholyl) was first reported by Guarneri and Evans[86] as useful in diagnosis in a patient with pheochromocytoma. Subcutaneous administration of 25 mg. of Mecholyl resulted in a slight fall of blood pressure from a basal level of 104/80 mm. Hg, followed in two minutes by rise to 210/140 mm. Hg. Their case also manifested all the symptoms characteristic of a paroxysmal attack of hypertension. In addition, the patient experienced other reactions to Mecholyl, including nausea, salivation, lacrimation, sweating, and dyspnea. To obtain information regarding the specificity of the test, it was performed on 27 additional patients from 20 to 60 years of age. In two of the hypertensive individuals, the test had to be terminated with atropine at the end of ten minutes, one because of a convulsive seizure. Such an eventuality is usually due to hypotension and/or heart block. They reported that atropine abolished the muscarinic reaction of Mecholyl, but did not influence the rise in blood pressure in a positive test. Mayock and Rose,[87] using 10 mg. of Mecholyl, reported a positive response in one patient with pheochromocytoma. Since the test is somewhat unreliable and may precipitate a fatal paroxysm, its routine use must be considered to be unjustified. Because of the severe muscarinic responses, the dosage should not exceed 10 mg., and previous atropinization of the patient is mandatory.

OL.
6
957

DEPRESSOR RESPONSE TO ADRENOLYTIC DRUGS

Another group of pharmacologic agents derives its usefulness from the inhibition of the pressor response in patients with pheochromocytoma, three-fourths of whom have sustained hypertension. Benzodioxane, Dibenamine, and phentolamine (Regitine) have been used to determine the presence of increased pressor substances.

BENZODIOXANE

Fourneau and Bovet[88] investigated the benzodioxane compounds in 1933, and first described their adrenolytic properties. Goldenberg and others[89] used piperidyl methyl benzodioxane intravenously in 4 patients with hypertension due to pheochromocytoma. They found that in these patients, as well as in normal patients with hypertension induced by the intravenous infusion of epinephrine, the drug had a predominately depressor action. In blood pressure elevations due to other causes, no depressor effect was produced by the drug. This was also reaffirmed by Shapiro and associates.[89a] The dosage recommended is 0.25 mg. per kilogram up to a maximum dosage of 20 mg.[90] This is given intravenously over a period of 2 or 3 minutes. During and following the injection, the blood pressure is recorded at ½ minute intervals for 3 to 5 minutes and then at 1-minute intervals, until the pressure returns to the previous level. Drill[91] observed flushing, palpitation, nervousness, cold and clammy extremities, mild headache, fright, sighing, and dizziness when the injection time was 30 seconds. These symptoms diminished if the period were increased to two minutes. The agent has caused alarming pressor responses in patients with primary hypertension, and there are reports of similar responses in cases of pheochromocytoma.

Chapman and Singh[84] state that the criteria for positive tests are a systolic depressor response of 30 mm. of mercury or more, and a diastolic pressure fall of 20 mm. or more, the maximum fall occurring promptly within 1 to 4 minutes after the start of the injection. They have reviewed the literature since 1949, and have found 22 cases of proved pheochromocytoma in which the benzodioxane test has been adequately reported. There were unequivocally positive results in 15 patients, equivocally positive results in 4 patients, and false negative results in 3 cases. They recorded a high incidence of false positive tests in patients with uremia and recommended that such cases not be subjected to the tests. No sedatives or narcotics of any kind should be administered during the 24 hours preceding the test. They state, and others have also reported, that false negative tests occur and detract appreciably from the specificity of the test.[93,94]

DIBENAMINE

The use of Dibenamine in the diagnosis of pheochromocytoma was reported by Spear and Griswold in 1948.[95] The studies of Hecht and Anderson[96] and of Nickerson[97] indicated that it effects adrenergic blockade. The rise of arterial blood pressure due to epinephrine is apparently blocked, and there is an apparent partial blockade of the mechanisms controlling resting vascular tone. The rise in cardiac output, however, is not affected nor is sinus tachycardia, increased peripheral blood flow, or increased respiratory volume after injection of epinephrine. The test has proved unreliable because of the high frequency of depressor responses in patients with hypertension who do not have pheochromocytoma, and the prolonged pharmacologic effects. If used at all, it should be confined to suspected cases of pheochromocytoma with sustained hypertension and with a resting control blood pressure level of greater than 150/110. The same may be said of Dibenzyline.

PHENTOLAMINE (REGITINE)

The use of Regitine in the diagnosis of pheochromocytoma has been recently recommended by Iseri, Henderson, and Derr.[98] It is a potent, relatively nontoxic, adrenergic blocking agent of comparatively high specificity. In the absence of uremia, or if the patient is not receiving sedatives or antihypertensive therapy, a positive response is strongly suggestive of pheochromocytoma.

Emlet and co-workers[94] and Gifford, Roth, and Kvale[99] have standardized the Regitine test and recommend that 5 mg. be given instantaneously by the intravenous route. Higher dosages are said to give false positive results. The criterion for a positive result is a fall in systolic pressure exceeding 35 mm. and a fall of the diastolic pressure exceeding 25 mm., occurring within 2 minutes of the intravenous injection. All positive results should be checked with the histamine test, if feasible. False positive tests have been reported by Ross,[100] Gifford, Roth, and Kvale,[100a] and Enderle and his colleagues.[101] If essential hypertension coexists with pheochromocytoma, an intramuscular injection may not cause an abrupt drop in the blood pressure. The only side effect of the intramuscular test dose may be moderate tachycardia. The intravenous test

may cause tachycardia, as well as weakness, dizziness, or flushing. A marked pressor response to Regitine and other tests has been reported by Wingo, Williams, and Wade.[102] As a routine screening test, Regitine appears to be the best drug available at present as it is more pleasant to the patient, safer, and easier to administer. The patient should be kept at rest following the test until orthostatic hypotension, if present, subsides.

MEASUREMENTS OF EPINEPHRINE AND NOREPINEPHRINE IN THE URINE AND BLOOD

Goldenberg and his colleagues[103] have studied the urinary secretion of catechol amines in 16 cases of pheochromocytoma, in cases of Addison's disease, in normotensive healthy subjects, and in essential hypertension. They found that, in the patients with pheochromocytoma, excessive urinary excretion of epinephrine and norepinephrine could be demonstrated both in persistent and in paroxysmal hypertension in the latter case, either during or between attacks. It may be necessary to collect urine before and during the occurrence of a spontaneous or induced attack of paroxysmal hypertension. By absorption of the urinary catechol amines on precipitated aluminum hydroxide, they studied extracts by bioassay, paper chromatography, photofluorometric evaluation, and absolute quantitation of norepinephrine and epinephrine chemically. In pheochromocytoma, they found that the most reliable test was photofluorometric evaluation of the urine extracts. They have devised a short photofluorometric procedure which is used as a rough screening test. When positive results are obtained, a longer and more specific method has been applied. With the latter, they have not as yet encountered a false positive result.

Rosenheim[104] believed that an estimation of the output of the catechol amines in the urine is probably the surest method now available for substantiating or refuting the diagnosis. Over a period of 18 months, he screened 100 selected patients with severe hypertension and found one pheochromocytoma. Since there may be a ten to fifty fold increase in the daily urine excretion of norepinephrine and epinephrine in patients with pheochromocytoma, according to von Euler,[105] the method may prove to be the most specific available in the diagnosis of pheochromocytoma.

The usefulness of the direct measurement of blood epinephrine and norepinephrine in patients with pheochromocytoma has been discussed by Lund.[106] His method does not seem to have the practical advantages of urine catechol amine determinations. Ödman's[105] method of percutaneous angiography allows precise estimation at selected sites.

TREATMENT

The only definitive treatment of pheochromocytoma consists of removal of the tumor(s).[30-32,107-122]

The surgical team, which includes a cardiologist, must be prepared before the operation begins for one or more of a number of crises peculiar to the tumor and described above. These include disturbances in physiology induced by: (1) release of varying amounts of epinephrine or norepinephrine because of

inadequate psychologic preparation, unskilled positioning of the patient, induction of anesthesia, or manipulation and removal of the tumor; (2) insufficiency of functioning adrenal, medullary,[122] or cortical tissue owing to destruction by the encroaching tumor or other pre-existing disease; and (3) the possibility of pneumothorax with ensuing hypoxia.

Hypoxia, which may be as potent a stimulant to adrenal medullary secretion as is tumor manipulation, must be avoided, as must agents which, in the presence of epinephrine, produce serious ventricular arrhythmias. Cyclopropane, chloroform, and ethyl chloride are unwise selections,[115,118,120] basal avertin and ether-oxygen probably being the safest and most suitable. Ether itself has induced an attack according to the DeCourcys.[30]

Because of the definite possibility that these tumors may be multiple, and because of the marked variation in their locations, a transverse abdominal approach is recommended, although it is recognized that pheochromocytomas have been removed successfully through many different routes. The entire abdomen should be explored, if feasible.

When adrenal involvement is unilateral or when the tumor is extra-adrenal, adrenal cortical insufficiency probably does not exist except in those patients with pre-existing cortical disease. One must always consider the possibility that the neoplasm may involve the only functional adrenal or that bilateral (16 per cent) tumors may exist. Any preoperative signs of relative cortical insufficiency place the prophylactic use of cortical principles on a rational basis.[122] It has been found that patients from whom practically all cortical tissue has been removed have been satisfactorily managed by 200 mg. of cortisone administered daily pre- and postoperatively.[122]

Preoperative quinidine in the hands of Ross and co-workers[123] did not prevent the development of cardiac arrhythmias. Electrocardiographic tracings during operation showed sinus tachycardia, nodal rhythm, auriculoventricular dissociation, paroxysmal ventricular tachycardia, numerous ectopic beats (multifocal ventricular, nodal, and auricular in origin), and incomplete and complete auriculoventricular block. Their well-documented report includes the successful management of cardiac arrest in one of their patients. The death of a quinidinized patient following adrenergic blockade with Dibenzyline, has been reported.[124] The action was thought peculiar to the drug under study, however, and independent of other effects.

At any point during management,[125] acute left-sided cardiac failure, shock, adrenal apoplexy,[126] or cardiac arrhythmias may supervene. The necessity for the preoperative establishment of partial adrenergic blockade with at least 5 mg. of phentolamine is well recognized, and intubation should be carried out only after this stage. The availability of two bottles of 5 per cent dextrose in water is essential, one liter containing 4 mg. of norepinephrine, the other, 32 mg. These are arranged in a system including a three-way stopcock near the hub of a large bore needle installed in an adequate free-flowing vein. At least 1,500 c.c. of compatible blood must be on hand, as well as adequate amounts of pitressin,[34] Neosynephrine,[127] epinephrine,' levarterenol, and hydrocortisone[128] for immediate intravenous use.

The most critical phase of the procedure is encountered when the tumor site is approached. The vascularity and contiguity of surrounding structures usually precludes total ligation of the mass, and the first of two major complications may arise at this point—marked hypertension may supervene which, if prolonged, necessitates the use of phentolamine in such amounts as to produce essentially complete adrenergic blockade. Total ligation of the tumor, or removal, almost invariably precipitates the second of the two possible complications—a profound hypotension. When this occurs, norepinephrine is required, often in enormous dosages. If the effect of norepinephrine has been abolished by previous adrenergic blockade, Neosynephrine or other pressor amines must also be instantaneously available.[127] In critical situations, the vasopressor action of pitressin in dosages of 0.5 to 1.0 mg. intravenously may have to be resorted to, and its coronary vasoconstricting properties weighed against the emergency confronting the team. Adrenergic blockade does not influence the vasoconstrictor action of this agent.

If neither of these complications occurs, the tumor should be presumed inactive, and a thorough abdominal exploration executed. Should no further tumors be seen and should an intravenous adrenolytic test with 5 mg. of phentolamine prove negative, the operation must be considered to be complete. If the catechol output of the tumor has been great, necessitating inordinate adaptation by the patient, sudden withdrawal of the source will necessitate postoperative substitution therapy in quantity for long periods. The rate of administration of the norepinephrine infusion will be indicated by the blood pressure response and other signs, and the determination may have to be made at quarter-hour to hourly intervals for days. Such pressor support can be abandoned only after physiologic stability is assured.

SUMMARY

Some of the greatest advances in modern medicine can be said to involve those reflected in the diagnosis and treatment of pheochromocytoma. Our knowledge of pheochromocytomas is now sufficient to permit a diagnosis by the thoughtful physician in nearly all cases. Though agreement on the management during the surgical phase cannot be wholly uniform, insight into the disturbances in physiology which circulating epinephrine and norepinephrine evoke, awareness of the alterations in homeostasis which follows excision of the tumor, and familiarity with the pharmacology of adrenergic blockade now assure immediate, specific, and effective action by the surgical team.

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VOL
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195

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OL.
6
957

Review

THE HUMAN HEMOGLOBINS

A. H. TUTTLE, B.S., M.S., M.D.*

MEMPHIS, TENN.

From the Division of Pediatrics, University of Tennessee College of Medicine, the LeBonheur Children's Hospital, and the Frank T. Tobey Memorial Children's Hospital, Memphis, Tenn.

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VOL
6
195

INTRODUCTION

ASSOCIATION of abnormal hemoglobin synthesis with a clinically discrete disease, sickle cell anemia, was first established by Pauling and associates[1] in 1949. Although a number of clinical and hematologic features of sickle cell anemia had been recognized for many years and Hahn and Gillespie[2] had concluded that the state of hemoglobin, i.e., oxygenated or reduced, was important in the sickling process, Pauling's discovery of the abnormal electrophoretic characteristics of "sickle cell" hemoglobin is directly responsible for the present concept of sickle cell anemia as a "molecular" disease.

The rapidly expanding interest in the relationship of inherited abnormalities in hemoglobin synthesis to human disease may be said to have originated with Pauling's discovery. During the past 8 years an enormous amount of fundamental and clinical research has been carried out in this field, resulting in significant contributions in hematology, biochemistry, genetics, anthropology, and clinical medicine. Many varieties of atypical human hemoglobins have been discovered and, in some instances, the clinical disease associated with a specific error in hemoglobin synthesis has been extensively studied and reasonably well defined. For the most part, our knowledge of the biologic effects of abnormal hemoglobin synthesis is incomplete, particularly with reference to the more recently described varieties.

In the following review an attempt is made to present the more outstanding characteristics of the various human hemoglobinopathies. For more detailed information the reader is referred to recently published reviews dealing more completely with certain facets of this subject.[3-10]

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TERMINOLOGY

Reference to the different varieties of human hemoglobin will be made in accordance with recommendations of the Hematology Study Section of the United States Public Health Service.[11] It is generally agreed that there are two types of normal human hemoglobin, designated as Hgb F and Hgb A, referring to the type predominating in fetal and in adult life, respectively. A third type, Hgb P, was found in early fetal life by Allison.[12] Abnormal varieties of human hemoglobin have been designated according to letters of the alphabet beginning with the letter *C*, omitting *B*, since the abnormal hemoglobin of sickle cell anemia had previously been referred to as "Hgb b." The list is now complete through Hgb J. Recently another previously undescribed hemoglobin was found by Robinson and associates,[13] which they designated provisionally as "Liberian 2."

In instances in which two types of hemoglobin are synthesized by the same individual it has been customary to refer to the combination in terms of the alphabetical names of both hemoglobins, the constituent present in highest concentration being first. For example, in sickle cell trait in which Hgb A predominates over Hgb S the combination is designated Hgb AS.

OL.
6
957

GENETIC ASPECTS OF HEMOGLOBIN SYNTHESIS

Normal Fetal and Adult Hemoglobins.—Present knowledge indicates that production of the normal human hemoglobins (P, F, A) is under the influence of nonallelic genes.[12] Synthesis of the primitive embryonic pigment, Hgb P, occurs in early intrauterine life.[12] In later fetal life, the predominance of Hgb F production suggests a high degree of influence of the gene for fetal hemoglobin. Suppression of this gene is almost complete in normal children and adults as indicated by the progressive reduction in fetal hemoglobin concentration beginning in fetal life and continuing throughout the first year of life coincidental with an increasing concentration of Hgb A. After this time, traces of Hgb F may be demonstrated by the alkali denaturation technique[14] and by immunologic methods in many normal individuals.[15,16] The apparent suppression of the gene for Hgb F synthesis may be influenced by a number of factors resulting in continuation of Hgb F production beyond the usual time or in reappearance of significant concentrations of Hgb F in peripheral blood later in life. Elevated Hgb F concentration has been found in association with untreated pernicious anemia, chronic aregenerative anemia, acute and chronic leukemia, myelophthisic anemia, hereditary spherocytosis, thalassemia,[14] and in certain diseases associated with abnormal hemoglobins discussed below.

Synthesis of abnormal hemoglobin is believed to occur as a result of the inheritance of a specific gene (or genes) which is an allele of the gene responsible for production of Hgb A.[17-19] It seems likely that introduction of these abnormal genes into human populations has occurred as a result of spontaneous genetic mutation, although in some instances mutation alone probably will not suffice to explain the frequency of occurrence of an abnormal hemoglobin in a population.[20]

Heterozygous Normal: Abnormal Hemoglobin Combinations.—The individual who has inherited the gene for Hgb A from one parent and a gene for abnormal

hemoglobin from the other parent is said to be a carrier or heterozygote for the particular type abnormal hemoglobin, or to have the abnormal hemoglobin trait. In the absence of other inherited abnormalities of the erythrocyte such as thalassemia, expressivity of the gene responsible for abnormal hemoglobin synthesis is less than that of the gene responsible for Hgb A production with the result that Hgb A comprises more than the expected 50 per cent of total hemoglobin. Exceptions to this usual finding are Hgb J carriers[13,21] in whom the concentration of the J component was found to be greater than Hgb A. In some individuals, suppression of the abnormal gene may be so marked that the abnormal hemoglobin is produced in extremely small quantities. Singer[22] has studied one case in which the peripheral blood of a carrier of Hgb S contained only 5 per cent Hgb S and erythrocyte sickling could not be demonstrated. The possibility that complete suppression (or a low degree of penetrance) of a gene for abnormal hemoglobin synthesis may occur in carrier states has been suggested. In this case an individual would be able to transmit the abnormal gene to an offspring yet would have no detectable abnormal hemoglobin.[23] This possibility is of obvious importance in medicolegal cases involving parentage disputes. In heterozygous carriers of abnormal hemoglobins the combination of an abnormal plus a normal hemoglobin gene appears to exert the same suppressing effect upon the nonallelic gene for Hgb F as in the normal individual. Consequently, elevated levels of Hgb F are not found unless other hematologic abnormalities are present also.

Homozygous Abnormal Hemoglobin Combinations.—In the event that an individual receives identical abnormal allelic genes from each parent, homozygosity for that particular abnormal hemoglobin results. In some instances abnormal allelic genes of Hgb A in the abnormal homozygote do not suppress Hgb F synthesis as effectively as in normal individuals or in carriers, resulting in significant production of Hgb F and an elevation of Hgb F concentration. This is most frequently observed in subjects with homozygous Hgb S disease.

Heterozygous Abnormal: Abnormal Hemoglobin Combinations.—As in the homozygote, these individuals do not possess the gene for Hgb A. In contrast, however, their hemoglobin consists of two abnormal species, the synthesis of each depending upon the inheritance of a different abnormal gene from each parent. Each component is usually present in approximately 50 per cent concentration.[7,24] Significant elevation of Hgb F levels are occasionally observed indicating incomplete suppression of the nonallelic gene for Hgb F.

Interaction of Inherited Abnormal Hemoglobins With Other Genetically Determined Hemolytic Anemias.—The gene responsible for thalassemia is thought to be nonallelic with the gene for Hgb A production and thus nonallelic with those for abnormal hemoglobins.[25,26] The inheritance pattern of thalassemia is similar to that of the abnormal hemoglobin syndromes in that the affected individuals may be heterozygous carriers or homozygotes. In addition, any of the above described abnormal hemoglobin combinations may, theoretically at least, occur in combination with either the thalassemia trait (thalassemia minor) or homozygous thalassemia (thalassemia major). The wide spectrum of clinical and hematologic manifestations of thalassemia and combined thalassemia: abnormal hemoglobin diseases indicates that the genetic interrelationship between the thalas-

semia gene and the genes associated with hemoglobin synthesis are quite complex. The ability of the thalassemia gene to suppress Hgb A formation (or to enhance Hgb F formation) results in elevated Hgb F levels in thalassemia major and in some of the combined thalassemia: abnormal hemoglobin syndromes.[26-29] The relatively high (above 50 per cent) concentration of the abnormal hemoglobin component in combined thalassemia: abnormal hemoglobin trait diseases is also believed to result from the suppression of Hgb A synthesis (or an enhancing effect upon expressivity of the abnormal gene) by the thalassemia gene allowing predominance of the abnormal hemoglobin.[26,29,30]

METHODS OF STUDY

With certain few exceptions no single laboratory determination serves to identify definitely an abnormal hemoglobin. Consequently, a number of different procedures have been utilized in studying fundamental properties of the various types of hemoglobin and in differentiating these hemoglobins one from the other. The description of some of these techniques which follows is not intended to provide the reader with instructions for performing the determinations but rather to describe briefly the principles involved and to indicate their relative usefulness in the diagnosis of the various abnormal hemoglobin states.

Usual Laboratory Procedures.—In this section will be listed ordinarily available laboratory determinations, the results of which may lead one to suspect an abnormal hemoglobin state and which in some cases may establish the diagnosis. Specific abnormal alterations reflected by these procedures will be given in the section dealing with a description of each of the inherited hemoglobinopathies.

1. Examination of appropriately stained peripheral blood smears with special attention to erythrocyte size and shape, staining characteristics, presence or absence of intraerythrocytic inclusions, nucleated red cells, and per cent reticulocytes.
2. Determination of leukocyte and erythrocyte counts, packed cell volume and hemoglobin concentration, and derivation of the values for MCV, MCHb, and MCHb concentration.
3. Bone marrow examination with special attention to erythyroid hyperplasia or hypoplasia.
4. Determination of erythrocyte osmotic fragility using hypotonic saline.
5. Specific test for sickling using a reducing agent such as sodium dithionite[31] and examination of venous blood collected anaerobically for number of sickled cells.[32]
6. Urine examination with special attention to low-fixed specific gravity, hematuria.
7. Determination of one minute and total values for serum bilirubin.
8. Quantitative determination of the daily output of stercobilinogen.
9. Roentgenograms of long bones and skull.

Electrophoresis.—The most commonly employed and perhaps the most valuable single procedure, electrophoresis, depends upon the fact that differences in amino acid composition and in configuration of the polypeptide chains[1,33] in the globin moiety of different types of hemoglobin result in variations in the net elec-

trical charge of the different molecular species when in buffered solution. When these molecules are suspended in a buffered environment in which freedom of movement is possible and an electrical current is passed through the environment, each hemoglobin molecule moves in a predetermined direction at a predetermined velocity toward the anode or cathode. Similar molecules exhibit similar directional and mobility characteristics and separate more or less completely from molecules of another species. The moving boundary technique of electrophoresis was first used in the study of human hemoglobins by Pauling and associates,[1]

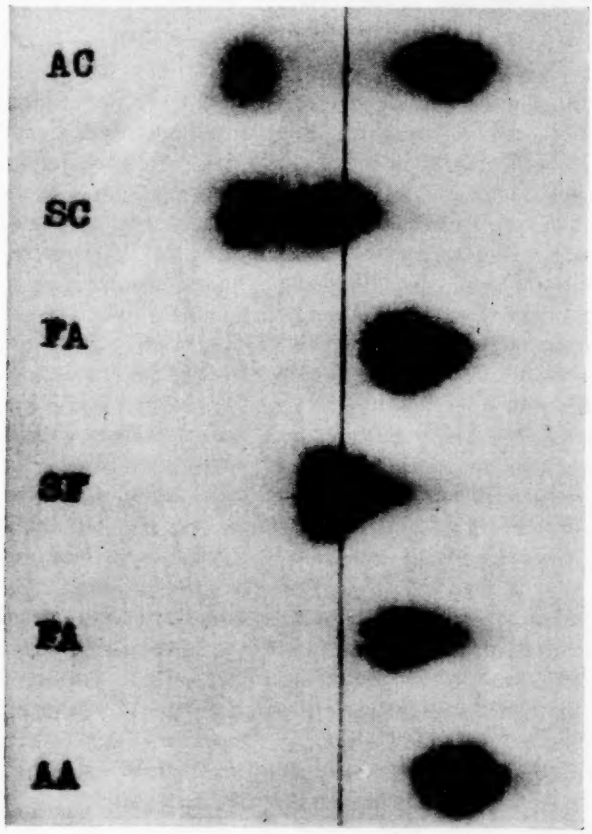

Fig. 1.—Electrophoretic record obtained using Munktell No. 20 filter paper, phosphate buffer, 0.08 molar, pH 7.4. Filter paper sheet was encased between glass plates. Anode is to the right.

who found that the electrophoretic characteristics of Hgb S were such that it could be separated from Hgb A. Moving boundary electrophoresis, while one of the most precise techniques used in the study of hemoglobin, is not generally adaptable to use as a procedure in large-scale studies because of the time and technical skill required for the determination and the expense of equipment. Development of a relatively simple, inexpensive method of performing electrophoretic separations of serum proteins using filter paper as an anticonvectant

supporting medium[34] and the subsequent application of this technique to the study of hemoglobins[35] has provided an invaluable tool in the study of the hemoglobinopathies and the means whereby most of the known hemoglobins have been discovered. Although reasonably simple in principle, reduplicable and consistently reliable results in paper electrophoresis are possible only when strict experimental conditions are observed. It is necessary that interpretation of paper electrophoresis records be made with proper consideration to such variables as buffer pH, method of preparation of hemoglobin solutions, apparatus employed, and methods of quantitative interpretation used such as photometric scanning of the record, staining, and elution. Itano, Bergren, and Sturgeon[9] have recently presented an excellent review of the subject of paper electrophoresis of hemoglobins including a description of the different types of apparatus and techniques which have been employed.

OL.
6
957

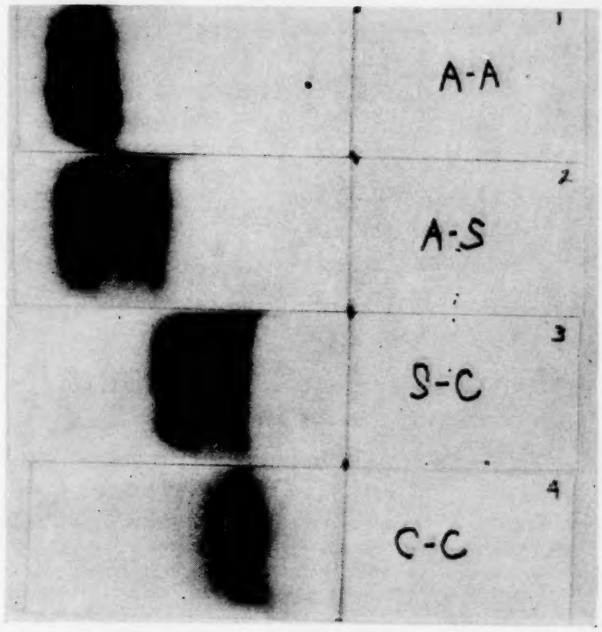

Fig. 2.—Electrophoretic record obtained using Whatman 3 mm. filter paper strips, one inch in width, and veronal buffer, 0.06 molar, pH 8.6. Strips were suspended in horizontal position on small plastic points. Anode is to the left.

In Fig. 1 is shown an electrophoretic record obtained on a number of naturally occurring hemoglobins. Despite the obvious difference in mobilities of Hgb F and Hgb A, mixtures of these two hemoglobins separate incompletely when analyzed by paper electrophoresis. In Fig. 2 is shown the electrophoretic separation of hemoglobins using a different technique.

Inert supporting media other than filter paper have been successfully used in studying the electrophoretic characteristics of hemoglobin such as starch,[36]

agar,[37] and cellulose powder.[37] The advantage of using these materials rather than filter paper is that a larger volume of hemoglobin solution may be analyzed and that in using starch and agar, adsorption and trailing is reduced. Following separation, individual isolated components may be recovered by elution for further studies.[38]

Kolin has described a method of electrophoresis in which individual proteins separate according to their respective isoelectric pH.[39] We have successfully applied this principle to the separation of hemoglobins.[40] Separation of various types of human hemoglobin is shown in Fig. 3. The separation has taken place

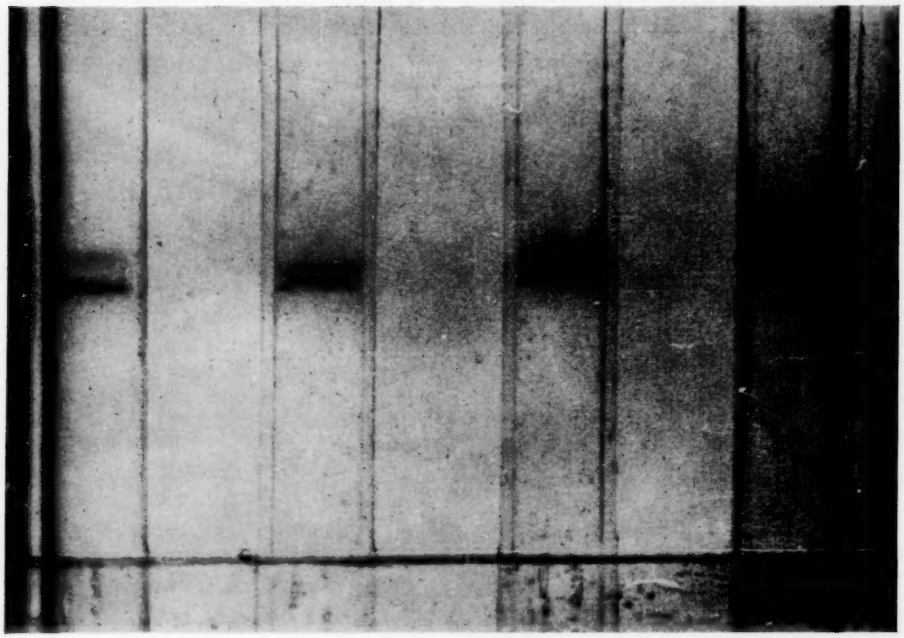

Fig. 3.—Separation of hemoglobin species according to isoelectric pH. The mixtures from left to right and from above downward are *CA*, *SA*, *CSA*, and *CS*. (From Tuttle: J. Lab. & Clin. Med. **47**:811, 1956.)

in vertical tubes in which pH and density gradients have been established. The position of individual hemoglobin bands from above downward is in order of decreasing isoelectric pH. Others have used the principle of isoelectric separation in carrying out paper electrophoresis.[41,42]

Fig. 4 is an idealized diagram showing the relative mobilities on filter paper of the known varieties of human hemoglobin using veronal buffer at pH 8.6, 0.05 ionic strength. The hazard of relying upon electrophoresis alone in the diagnosis of abnormal hemoglobin diseases is apparent since certain different hemoglobins exhibit identical mobilities at a certain pH. Electrophoretic studies at a more acid pH of 6.5 have shown that Hgb H may be differentiated from Hgb I since

the former moves toward the anode and the latter toward the cathode.[43] Furthermore, at pH 6.5 in moving boundary electrophoretic studies Hgb E more nearly resembles Hgb S, while at pH 8.6 using paper electrophoresis it more nearly resembles Hgb C.[44] Further procedures valuable in differentiating electrophoretically similar species of hemoglobin are described below.

Alkali Denaturation.—The outstanding characteristic of fetal hemoglobin, Hgb F, is its resistance to denaturation by alkali, a property which is shared by no other known human hemoglobin. The historical background of denaturation experiments has recently been reviewed.[5,9] The most widely applied technique for the demonstration and quantitative determination of alkaline-resistant hemoglobin is that described by Singer, Chernoff, and Singer.[14] Essentially the method consists of exposing a known quantity of hemoglobin to a solution of N/12 KOH (pH 12.7) for exactly one minute during which hemoglobins other than F are completely denatured. Following this interval, the solution is neutralized and the denatured hemoglobin precipitated by 50 per cent saturated $(NH_4)_2SO_4$. The amount of undenatured hemoglobin remaining in solution is then determined and expressed as per cent of the original hemoglobin, i.e., per cent alkaline-resistant hemoglobin. This procedure is particularly useful in detecting small amounts of fetal hemoglobin in mixtures containing other electrophoretically similar hemoglobins such as A and G.

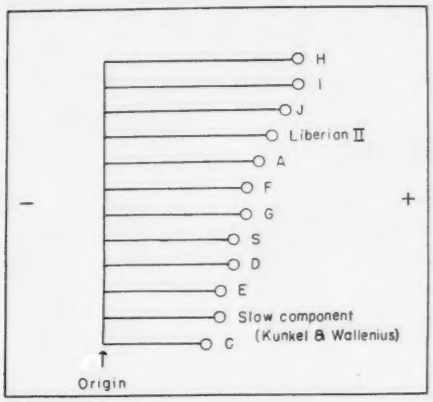

Fig. 4.—Relative mobilities of known human hemoglobins on filter paper using veronal buffer, 0.06 molar, pH. 8.6.

Solubility Determination.—Although a tedious procedure and one requiring utmost attention to experimental conditions, determination of the solubilities of reduced hemoglobins has proved to be a valuable method for differentiating Hgb S from Hgb D, their electrophoretic mobilities being identical.[45] The insolubility of reduced Hgb S in aqueous solutions of certain inorganic salts is a property possessed only by this particular hemoglobin.[46] Reduced Hgb C has been found to be more soluble than Hgb A.[47] while the solubility of Hgb G in the reduced state is intermediate between Hgb A and Hgb S.[48]

Chromatography.—Using a finely divided ion exchange resin (IRC-50[XE-64]) Huisman and Prins[49] separated carboxyhemoglobins A, C, F, and S. The sep-

arated components were clearly visualized in the column. By varying the technique somewhat they were able to recover almost completely the individual hemoglobins. Other reports of separation of hemoglobins by chromatographic methods have also appeared in recent years.[50,51] Using the resin IRC-50(XE-64) and by means of gradually increasing sodium ion concentration in the eluant, Morrison and Cook separated Hgb A into three components.[51] Dr. Kozo Nishimura, working in our laboratory, has recently repeated the experiments reported by the latter authors and has obtained results similar to theirs. Fig. 5,*A* shows the separation of the three components of Hgb A, the hemoglobin concentration being plotted against consecutively collected eluant fractions. Separation of a mixture of Hgb S and C is shown in Fig. 5,*B*. Factors governing the chromatographic

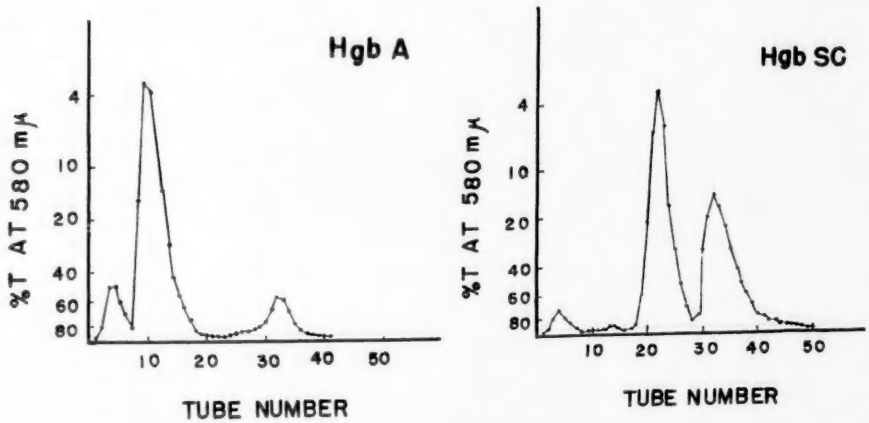

Fig. 5.—*A*, Fractionation of Hgb A by column chromatography. *B*, Fractionation of Hgb SC mixture by column chromatography. The first small peak (fractions 2-6) may represent fetal hemoglobin. Subsequent electrophoretic analysis revealed the highest peak to represent Hgb S and the last major peak (fractions 29-40) Hgb C.

characteristics of hemoglobin are largely unknown. The possibility that the apparent heterogeneity of Hgb A when studied in this manner may be due to varying degrees of denaturation or other chemical alterations in the hemoglobin molecule has not been ruled out.[5] Recently Kunkel and Wallenius[38] have described two electrophoretic components other than the major fraction of Hgb A in blood obtained from normal adults and from adults with a variety of anemias. One of the components (Fig. 4) exhibited an electrophoretic mobility similar to Hgb E in a variety of buffers and comprised from 1.8 to 3.5 per cent of the total hemoglobin. This component was reduced or absent in blood obtained from newborn infants. A second component exhibited an electrophoretic mobility somewhat greater than the major fraction at pH 8.6.

Other Methods.—Hemoglobins have been studied by a variety of other methods which are of value primarily in defining some of their fundamental physical and chemical properties rather than in identifying abnormal types of hemoglobin. These include crystallographic,[52] spectrophotometric,[52,53] and x-ray diffraction

studies,[46] determination of monomolecular film spreading velocity,[54] amino acid composition,[55,56] and oxygen dissociation curves.[57-59]

We have demonstrated[37] that stroma of cells containing a high per cent Hgb S exhibits an unusual affinity for methylene blue. This appears to be an adsorptive phenomenon, similar to but more marked than the increased affinity for methylene blue exhibited by erythrocytes of newborn infants reported by Smith.[60] The significance of this peculiar property is at present unknown.

Immunochemical methods provide extreme sensitivity in detecting the presence of Hgb F,[15,16,61,62] but have not been of value in identifying other types of hemoglobins.

Determination of in vivo survival of erythrocytes containing abnormal hemoglobin has in certain instances provided proof of the excessive rate of hemolysis of the abnormal cells. Specific references will be made to erythrocyte survival studies in the discussion which follows.

VOL.
6
1957

MANIFESTATIONS OF ABNORMAL HEMOGLOBIN SYNTHESIS

I. *Heterozygous Normal: Abnormal Hemoglobin Combinations.*—

Hemoglobin S trait (AS): Hemoglobin S is the most frequently encountered abnormal hemoglobin in this country and certain other areas of the world. The incidence in American Negroes is approximately 9 per cent.[63,64] It has been found in India,[65] Turkey,[66] Greece,[67] Italy,[25,68] and in Africa.[69,70] The incidence in Africa varies from tribe to tribe, in some areas as high as 45 per cent.[64,70]

Other than exhibiting the sickling phenomenon, erythrocytes are normal, and affected individuals usually have no abnormal clinical findings. Exceptions are reported instances of massive hematuria[4,64,71] and of splenic infarction at high altitudes.[72] Certain of these individual patients were later found to have combined abnormal hemoglobin diseases, others definitely had sickle cell trait.[73] Hematuria apparently results from local hypoxia, sickling of susceptible cells, stasis, and parenchymal necrosis. Hyposthenuria, a defect in the urine concentrating ability of the kidney, has been reported in subjects with sickle cell trait,[74,75] although not to the degree seen in patients with homozygous Hgb S disease.[75,76]

In individuals with sickle cell trait, Hgb S is present in concentrations of from 5 to 50 per cent averaging about 30 per cent.[22,77] Fetal hemoglobin is not elevated. The life span of erythrocytes of Hgb S trait individuals is normal.[78,79]

Hemoglobin C trait (AC): Carriers of Hgb C comprise 2 to 3 per cent of the American Negro population.[80,81] Affected individuals are clinically normal and discovery of the abnormal hemoglobin is usually the result of family studies in which one or more individuals have combined hemoglobin disease or homozygous Hgb C disease, or in large-scale population surveys. Erythrocyte count, hemoglobin concentration, and hematocrit values are normal.[82-85] There is usually a noticeable increase in target cells on peripheral blood smear, the frequency in one series ranging from 3 to 33 per cent.[85] In several instances the condition has been accurately suspected because of this latter feature. Great variation in the number of target cells, the lack of correlation between per cent target cells and per cent abnormal pigment, and the fact that related heterozygous Hgb C individuals exhibit similar numbers of target cells suggests that the occurrence of

target cells may be independently genetically influenced.[85] Electrophoretic analysis reveals the abnormal hemoglobin to be present in concentrations averaging approximately 35 per cent, the remainder being Hgb A.[80,82,86]

A shortened in vivo life span of Hgb AC erythrocytes was originally reported by Kaplan, Zuelzer, and Neel.[83] In a later communication they report normal survival times.[85] Others have also reported normal survival.[79]

Hemoglobin D trait (AD): Chernoff has recently emphasized the widespread distribution of Hgb D among different races and colors, a characteristic not shared by other abnormal hemoglobins.[87] He found a surprising frequency of occurrence of Hgb D trait in the American Negro. In surveying the hemoglobin types of 1,000 Negroes, four (or 0.4 per cent) were heterozygous for Hgb D. Although electrophoretically identical with Hgb S, Hgb D is more soluble in the reduced state[45] and its presence in the erythrocyte does not result in sickling at low oxygen tension. In individuals with Hgb D trait, Hgb A predominates, comprising more than 50 per cent of the total hemoglobin. This combination is not associated with other hematologic or clinical abnormalities.[45]

Hemoglobin E trait (AE): Hemoglobin E has been encountered chiefly in individuals of southeast Asian extraction, particularly from the state of Thailand where the incidence of Hgb E was found to be 13.6 per cent of the population of pure Thai or mixed Thai extraction.[29,44] In individuals with Hgb E trait, Hgb A predominates and no disabilities have been noted. Results of hematologic studies have been normal.[29,88-90]

Askoy and associates[90a] have pointed out that the slowly migrating hemoglobin component described by Kunkel and Wallenius[38] may be significantly elevated in patients with thalassemia and that such patients might be suspected of having Hgb E trait since the electrophoretic mobilities of the two pigments are identical. The authors emphasize, however, that the proportion of Hgb E in individuals with Hgb E trait is always above 20 per cent, whereas the proportion of the slow component in thalassemia is ordinarily less than 15 per cent of the total hemoglobin.

Hemoglobin G trait (AG): Only isolated reports of the occurrence of Hgb G are available. It has been found in African Negroes[48] and in one white family in this country.[91] According to Schwartz (quoted by Chernoff[4]) the presence of Hgb G in association with Hgb A does not result in any significant clinical disease. It seems quite possible that Hgb G carriers may have escaped detection in large-scale population surveys due to the absence of clinical evidence of disease and the fact that presence of the abnormal pigment might not be suspected in paper electrophoretic studies, i.e., because the mobility of Hgb G is the same as Hgb F.

Schwartz and co-workers[91a] have recently presented evidence which strongly suggests that Hgb G may be a normal variant of hemoglobin rather than an abnormal type of hemoglobin.

Hemoglobin H trait (AH): Rigas and co-workers[28] described an abnormal hemoglobin found in three members of a Chinese family which differed from previously described hemoglobins in several ways. The electrophoretic mobility at alkaline pH was greater than Hgb A and abnormal hemoglobins previously described. The abnormal pigment was found to undergo irreversible denaturation and to precipitate from solution on standing at room or refrigerator temperatures.

The latter property of the abnormal pigment was believed related to inclusion bodies seen in erythrocytes of affected patients and to the shortened erythrocyte survival time which the authors demonstrated. The inclusion bodies were seen in freshly drawn wet preparations of peripheral blood and were noted to increase with time so that at the end of 10 minutes all erythrocytes contained the inclusions. Other manifestations of the inherited abnormality included hypochromic microcytic anemia refractory to iron therapy, reticulocytosis, splenomegaly, and increased resistance of erythrocytes to hypotonic saline solution. Similarity of the peripheral blood picture to that seen in thalassemia and the fact that other members of the family were found to have hematologic abnormalities consistent with thalassemia minor suggested to the authors that the clinically affected subjects may have inherited the gene for thalassemia as well as a gene for abnormal hemoglobin synthesis.[23,92] The abnormal hemoglobin was observed in neither parent of the affected subjects. The possible interesting explanations for this finding were presented. Cabannes and co-workers[93] refer briefly to 3 cases of heterozygous Hgb H disease encountered in a large survey in Algeria. Hematologic and clinical data are not given in the abstract to which reference is made.

Hemoglobin I trait (AI): A second abnormal hemoglobin with an electrophoretic mobility greater than Hgb A in alkaline buffer has been designated Hgb I by Rucknagel, Page, and Jenson.[43] The pigment was present in combination with Hgb A in 6 asymptomatic members of a Negro family of 17. Hematologic values were all within normal limits except for an unexplained lymphocytosis in one of the affected individuals. Hemoglobin A comprised 80 per cent of the total hemoglobin, the remainder being Hgb I. This ratio was found to be approximately the same in all affected subjects. It was emphasized that differentiation of Hgb I from Hgb H requires electrophoretic studies using relatively acid as well as alkaline buffers.

Hemoglobin J trait (JA): Thorup and associates[21] described an abnormal hemoglobin with an electrophoretic mobility in alkaline buffer intermediate between Hgb A and the two other rapidly migrating pigments, Hgb H and Hgb I. The subject of their studies was a Negro female whose father and 5 of her 8 siblings were found to have the abnormal pigment. None of the affected persons had other evidence of hematologic disease, and of those available for study, none had clinical manifestations of disease which could be attributed to the presence of the abnormal hemoglobin. The solubility of a reduced Hgb J plus Hgb A mixture was found to be significantly higher than of Hgb A alone.

Recently Robinson and associates[13] reported the discovery of two rapidly migrating components on paper electrophoresis found during a survey of the hemoglobin types of Liberian natives. Electrophoresis at pH 6.5 showed the abnormal pigments to be different from Hgb H and Hgb I. One of these ("Liberian I") was electrophoretically identical with Hgb J and was found in 7 of 920 blood samples examined. The report was of a preliminary nature and complete hematologic data were not given.

It is interesting that electrophoretic studies of the Hgb J of Thorup[21] and the "Liberian I" (probably Hgb J) described by Robinson reveal the abnormal pigment to be present in concentrations of approximately 60 per cent of the total

hemoglobin. Other abnormal hemoglobins, unless associated with other erythrocyte abnormalities, rarely comprise even 50 per cent of the total hemoglobin when in combination with Hgb A.

Cabannes and his colleagues[93] report finding 8 cases of heterozygous Hgb J in Algeria. Three of these were double abnormal heterozygotes, Hgb J being found in association with Hgb D.

The "Liberian II" component described by Robinson[13] has not been assigned an alphabetical designation. It apparently represents a discrete abnormal hemoglobin, different from those previously discussed.

II. *Homozygous Abnormal Hemoglobin Combinations.*—

Hemoglobin S disease (SS): In the newborn infant who is destined to have Hgb SS disease Hgb F predominates as in normal infants and the per cent Hgb S is low. Concomitant with the reduction in Hgb F concentration there occurs a progressive increase in Hgb S. Abnormally high concentrations of an alkaline-resistant hemoglobin persist, however, throughout the life of the individual, comprising up to 40 per cent of the total hemoglobin, the remainder being Hgb S.[6,14,94] Singer[95] has shown that distribution of the two types hemoglobin, S and F, is inconstant among members of the erythrocyte population, i.e., that in some erythrocytes the predominant pigment is Hgb F, in others, Hgb S.

All clinical and hematologic manifestations of this disease appear to be intimately related to the property of erythrocytes containing sufficient Hgb S to undergo sickling under conditions of low oxygen tension. Consequently, manifestations of the disease are not ordinarily present during the period of infancy when the Hgb S concentration is comparatively low.[96] The sickling phenomenon is believed due to an unusual orientation of the abnormal hemoglobin molecules.[46,97,98] Harris[98] found that concentrated and deoxygenated solutions of Hgb S when examined microscopically exhibited surface phenomena which he refers to as "tactoid formation." The outline of these microscopic surface irregularities bore a remarkable resemblance to the outline of sickled erythrocytes. Harris suggested that the sickled erythrocyte represents a "hemoglobin tactoid thinly veiled and somewhat distorted by the cell membrane."

In venous blood 30 to 60 per cent of erythrocytes may be sickled.[32] The consequences of intravascular sickling are an unusually rapid rate of intravascular hemolysis due to the increased mechanical fragility[99] and capillary stasis and obstruction due to the rather rigid and unyielding structure of the sickled cells. The increased rate of erythrocyte destruction results in an uncompensated[100] hemolytic process manifest by low hemoglobin levels (usually less than 8 Gm. per cent), low erythrocyte count, reticulocytosis, hyperbilirubinemia, increased pigment excretion, erythrocytic hyperplasia of the bone marrow, and roentgenographic evidence of chronic bone marrow hyperplasia. Anemia is of the normochromic, normocytic type. Erythrocytes are unusually resistant to hemolysis by hypotonic saline. Sickled cells, basophilic stippling, nucleated red cells, and target cells are found on stained peripheral blood smears. An aplastic crisis in this disease may lead to an exaggeration of the already severe anemia, particularly during the course of infections.[7,101,102]

Functional and anatomic abnormality of practically every organ and organ system has been demonstrated in patients with homozygous sickle cell disease. The bizarre combinations of signs and symptoms presented by these individuals may suggest many other diseases. It is frequently difficult to decide whether the clinical signs of disease in these patients are the result of sickle cell anemia rather than another disease or sickle cell anemia in addition to another disease. Affected individuals are usually moderately physically retarded, pale, and frequently exhibit icterus of the sclera and mucous membranes. In children the abdomen may be protuberant and the spleen markedly enlarged. Splenomegaly is less often found in older children and adults due to the progressive fibrosis resulting from chronic vascular obstruction in that organ. Abnormal encephalographic records have been obtained in patients with no other evidence of neurologic involvement.[103,104] Cerebral vascular thrombosis is not uncommon, leading to more or less severe sequelae. The severe chronic anemia is associated with a marked increase in cardiac output.[105] Cardiac decompensation[7,106] and the occurrence of mural thrombi[107] have been reported in association with the disease. Systolic and diastolic murmurs and electrocardiographic changes are not uncommon, as in other types of severe anemia.[8,108] Painful fusiform swelling of the fingers and toes, occasionally swollen areas over other joints and other bony surfaces such as the forehead[37] may be prominent manifestations. As in other chronic hemolytic anemias, biliary calculi and chronic cholecystitis may occur. Severe abdominal pain suggesting a surgical disease may occur acutely and persist for days.[7,109] No satisfactory explanation has been given for the occurrence of these attacks. In some cases acute back and flank pain suggestive of acute renal colic due to calculi has been associated with massive hematuria.[110]

Although leg ulcers are encountered infrequently in children, older individuals are prone to develop chronic extensive ulceration of the skin of the lower extremities. The adjacent skin appears thin and atrophic. Treatment with skin grafts and local therapy such as pressure dressings offer only temporary relief.[109]

Striking bone changes may be demonstrable roentgenographically, such as the "hair on end" appearance of the skull, coarseness of the architectural pattern of other bones, and aseptic necrosis of the femoral head. Patients with Hgb SS disease appear to be unusually susceptible to osteomyelitis due to the Salmonella group of organisms.[111]

A defect in renal concentrating ability has been repeatedly observed in patients with Hgb SS disease.[74-76,112] It has recently been shown that this defect may be reversed in young individuals by transfusing large volumes of blood from normal donors but not in older children or adults.[75] We found marked increments in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity for para-aminohippurate in children and young adults with homozygous Hgb S disease.[113] After the age of 20 or 30 years, however, these functions were found to be progressively and seriously reduced.[114]

Other than symptomatic therapy no treatment has been found effective for the patient with Hgb SS disease. Transfusions should probably be reserved for those cases in which a precipitous reduction in hemoglobin concentration occurs, such as during acute infections or late in pregnancy.[7] Splenectomy is reported

by Singer[7] to have been of value in correcting thrombocytopenia in patients with splenic dysfunction, and Watson[8] found beneficial effects of splenectomy in patients with marked splenomegaly associated with evidence of hypersplenism. The procedure is of questionable value otherwise. Priscoline was found to give considerable relief from pain in children with abdominal symptoms attributable to sickle cell crisis but was less effective in relieving bone and joint pain.[115]

Hemoglobin C disease (CC): In contrast to the severe hematologic handicap imposed by the homozygous Hgb S combination, individuals with homozygous Hgb C disease fare rather well.[4,86,116-121] While primarily a disease affecting the Negro race, isolated cases have been reported in white individuals.[121] The life span of erythrocytes containing Hgb C is shortened, indicating a hemolytic process.[79,118,119] The increased rate of red cell hemolysis is, in most cases, compensated for by an increase in erythrogenesis sufficient to prevent severe anemia. A mild normochromic, normocytic anemia has been found in some cases. Slight elevations in serum bilirubin and in fecal urobilinogen reflect the increased rate of hemolysis. Examination of peripheral blood reveals a conspicuous increase in target cells, abnormally high reticulocyte counts, and, occasionally, nucleated red cells. Osmotic fragility is moderately decreased. Tetragonal crystals of hemoglobin were observed in the erythrocytes of individuals with Hgb CC disease in whom splenectomy had been performed.[121,122] In vitro crystallization of hemoglobin in erythrocytes containing predominately Hgb C has been reported in individuals with other combined abnormal hemoglobin: Hgb C diseases.[123] Fetal hemoglobin levels are usually normal. The spleen is quite large, occasionally necessitating splenectomy for the relief of the associated discomfort.[118] Arthralgia and abdominal crises have been reported but are uncommon.

Hemoglobin D disease (DD): Recently Chernoff and co-workers[124] have reported the first known case of homozygous Hgb D disease. The patient was a Negro with some white English and American ancestry. Although there was no anemia, the erythrocyte survival time was somewhat shortened. There was moderate erythrocytic hyperplasia of the marrow. Target cells were prominent and there was slight hypochromia and microcytosis. Electrophoretic analysis revealed a single component with a mobility identical with that of Hgb S. Erythrocyte sickling could not be induced and results of solubility studies further differentiated the abnormal pigment from Hgb S. Complete family studies were impossible, but on the basis of information obtained from the study of siblings, the authors conclude that the patient is homozygous for the abnormal Hgb D.

Hemoglobin E disease (EE): Thus far the only reported cases of homozygous Hgb E disease have been in natives of Thailand.[29,89] Hematologic studies revealed a mild microcytic normochromic anemia, normal reticulocyte count, increased numbers of target cells, increased resistance to hypotonic saline hemolysis, and a normal or slightly hyperplastic (erythrocytic) bone marrow. There was no subjective evidence of increased erythrocyte hemolysis. Splenomegaly and a history of arthralgia and easy fatigability were inconsistent findings. Although electrophoretic studies revealed the presence of only one pigment, Hgb E, an alkaline resistant pigment was demonstrable in concentrations up to 6.4 per cent.

Hemoglobin G disease (GG): Only one case of homozygous Hgb G disease has been reported.[48] The subject was free of clinical or hematologic abnormalities other than the presence of the abnormal hemoglobin on electrophoresis.

Individuals with homozygous hemoglobins H, I, and J have not been reported.

III. *Heterozygous Double Abnormal Hemoglobin Combinations.*—

Hemoglobin CS disease: The combination of Hgb S and Hgb C[7,24,80 83-85,125] may result in a disease resembling homozygous Hgb S disease in severity or may be found in the absence of hematologic or clinical abnormalities more than might be expected in either of the two abnormal hemoglobin traits. The two abnormal hemoglobins are usually present in approximately equal concentrations, with slight predominance of Hgb C.[7] Hgb F levels may be slightly elevated. A mild to moderately severe anemia usually results from the accelerated rate of erythrocyte destruction for which the bone marrow is unable to compensate. Erythrocytes are normochromic with numerous target cells. Elevated reticulocyte counts are found as a rule, and in severe cases nucleated erythrocytes may be found on peripheral blood smears. Intravascular sickling was found consistently by Singer[7] in patients with Hgb CS disease. Sickling always occurs in sickle cell preparations in which a reducing agent is employed. Subjective symptoms quite similar to those in patients with Hgb SS disease may be pronounced or practically absent. The spleen is usually enlarged. In one of our cases the glomerular filtration rate, effective renal plasma flow and tubular excretory capacity for para aminohippurate were markedly increased as in patients with Hgb SS disease. This patient has also had one episode of osteomyelitis due to an organism of the Salmonella group.

Hemoglobin SD disease: Sturgeon, Itano, and Bergren[126] have reported results of their studies on two young white adults whose mother had Hgb D trait and whose father had Hgb S trait, resulting in Hgb SD disease in the two offspring. The combination resulted in a mild hemolytic process and mild anemia. One of the subjects had clinical findings similar to those seen in Hgb SS disease, the other was asymptomatic.

Hemoglobin SG disease: Schwartz and co-workers[91a] have reported the results of their studies of a large family harboring the genes for Hgb S, Hgb G, and thalassemia. One individual was of the phenotype Hgb S: Hgb G and had clinically a sickle cell trait. On the basis of their findings the authors concluded that the gene responsible for Hgb G is not an allele of the gene for Hgb S synthesis and postulate that genes responsible for hemoglobin synthesis must be located at three (at least) different genetic loci.

Hemoglobin JD disease: While surveying hemoglobin types in Algeria, Cabannes and his co-workers[93] found 3 individuals with Hgb JD combination. Other hematologic and clinical data were not presented in the abstract.

IV. *Combined Thalassemia: Abnormal Hemoglobin Diseases.*—

Thalassemia (Mediterranean anemia, Cooley's anemia, hereditary leptocytosis) occurs as a result of an inherited genetic defect, the determinant genes being located at a site remote from the locus of the genes responsible for hemoglobin synthesis. Neel and Valentine[127] postulate that inheritance of the thalas-

semia gene from each parent results in the syndrome, thalassemia major, in the offspring (homozygous thalassemia) while thalassemia minor results if the offspring inherits the thalassemia gene from one parent and its normal allele from the other (heterozygous thalassemia). Singer and co-workers[7] have further classified the thalassemia syndromes as follows, based on erythrocyte characteristics and hemoglobin levels: (1) thalassemia major; (2) thalassemia intermedia; (3) thalassemia minor; and (4) thalassemia minima. Great variation in the clinical states resulting from inheritance of the thalassemia gene suggests a complicated system of genetic interrelationships[4] which is, so far, poorly understood. The thalassemia syndromes are most frequently encountered in individuals of Greek, Italian, and Syrian extraction but have also been reported in races other than those of Mediterranean extraction.[30,128-131] Manifestations of the thalassemia diseases depend upon a defect in erythrocyte structure[7,30] and possibly improper utilization of iron in hemoglobin synthesis.[132] Hematologic findings in thalassemia major include a severe hemolytic anemia with microcytosis, hypochromia, target cells, anisocytosis, and poikilocytosis. There is increased resistance to hemolysis by hypotonic saline. Hgb F concentration is significantly elevated and in some cases comprises almost 100 per cent of the total circulating hemoglobin. The above hematologic alterations are less marked in the other thalassemia syndromes, i.e., intermedia, minor, and minima.[7] In some instances manifestations may be so mild that presence of the thalassemia gene cannot be established with certainty. Since thalassemia, per se, is not associated with production of an abnormal hemoglobin, description of the clinical aspects of thalassemia is beyond the scope of this review. Other reviews dealing primarily with clinical manifestations are recommended.[133-135] Since the genes responsible for thalassemia and those responsible for hemoglobin synthesis are nonallelic, any of the thalassemia diseases may, theoretically at least, coexist with any of the abnormal hemoglobin syndromes. Only a few of the many possible combinations have been described.

Thalassemia: heterozygous Hgb S disease (microdrepanocytic disease): Patients with this combination[25,26,28,136-139] exhibit hematologic findings similar to those in thalassemia major, i.e., moderately severe hemolytic anemia, microcytosis, hypochromia, significant numbers of target cells, anisocytosis, poikilocytosis, and occasionally nucleated red cells in peripheral blood. The usual tests for sickling are positive. The hemoglobin is comprised of types S, A, and frequently F. Hemoglobin S predominates, being present in higher concentration than in patients with uncomplicated sickle cell trait. The per cent of fetal hemoglobin is variable but is usually significantly increased. The clinical manifestations which are also variable include hepatosplenomegaly, arthralgia, and occasionally episodes of mild abdominal pain. Aseptic necrosis of the femoral head has been reported.[140]

Thalassemia: heterozygous Hgb C disease: Individuals with this combined abnormality have been studied by Singer and his colleagues,[30] Zuelzer and Kaplan,[141] Erlandson, Smith, and Schulman,[142] and Motulsky and co-workers.[143] The subjects exhibited hematologic and clinical manifestations of widely varying degrees of severity. The disease has been reported in white persons as well as

in Negroes. A mild hemolytic anemia, microcytosis, increased numbers of target cells, and, in the more severe cases, reticulocytosis have been reported. The most pronounced effects were found in the case studied by Zuelzer and Kaplan.[141] The case reported by the latter authors is unusual in that Hgb C comprised only 29 per cent of the total, while in other reported cases Hgb C predominated with concentrations of 90 per cent being found in some instances.

Thalassemia: Hgb CS disease: Brown, Sprague, and Kloepfer[144] have studied 2 patients whom they believe to represent examples of this syndrome. The father of the subjects had thalassemia: Hgb C disease and the mother had sickle cell trait. Mild anemia, microcytosis, numerous target cells, and a mild hemolytic process were demonstrated. Fetal hemoglobin was not increased. Hemoglobins C and S were present with Hgb C predominating.

Thalassemia: Hgb Sg disease: This combination has been described in one patient by Schwartz and associates.[91a] Manifestations of the disease were identical with those resulting from thalassemia: Hgb S disease except that Hgb S comprised only 50 per cent of the total hemoglobin. In most instances in which thalassemia minor coexists with sickle cell trait (Hgb AS), Hgb S predominates. The authors conclude that "the presence of the thalassemia gene does not necessarily depress or suppress the formation of Hgb G in a manner analagous to its usual effect on the production of Hgb A in ordinary sickle-cell-thalassemia."

Thalassemia: Hgb E disease: Examples of this entity have been reported in individuals of Thai,[29,88] Indonesian,[145] mixed Indonesian-Dutch,[90] and mixed Guatemalan, Spanish, Hindu, and Italian extraction.[44] The combination results in a microcytic hypochromic anemia with polychromasia, reticulocytosis, significant numbers of nucleated erythrocytes in the peripheral blood, and occasionally up to 8 per cent spherocytes. Decreased erythrocyte survival time has been demonstrated. Electrophoretic and alkali denaturation studies revealed the presence of Hgb F and Hgb E. Chernoff[29] mentions the possibility that small amounts of Hgb A may have escaped detection by the techniques employed. Clinical manifestations are rather marked and usually begin before the age of ten years. Growth retardation and subjective symptoms such as shortness of breath, pallor, intermittent jaundice, and susceptibility to respiratory infections are characteristic. Cardiac enlargement and hepatosplenomegaly are usual findings.

Thalassemia: Hgb G disease: In a recent review Smith[10] refers to a personal communication from Spaet describing an Italian with this syndrome. Hypochromic red cells, target cells, basophilic stippling, slight reticulocytosis, and moderate anemia were found. Erythrocyte survival time was shortened.

Two individuals studied by Schwartz and associates[91a] were found to have thalassemia: Hgb G disease. Neither of the subjects had clinical or hematologic abnormalities differing significantly from those ordinarily associated with thalassemia minor. From their studies it is evident that the gene responsible for thalassemia is not an allele of the gene for Hgb G synthesis.

Thalassemia: Hgb H disease: A brief description is given by Motulsky and co-workers of this disease occurring in two unrelated Filipinos.[143] Hypochromic

anemia and shortened erythrocyte survival were found. Electrophoretic analysis revealed predominance of Hgb A. Hgb F was not increased.

V. *Combined Spherocytosis: Abnormal Hemoglobin Disease.*—

Spherocytosis: heterozygous Hgb S disease: The occurrence of this unusual combination has been reported by Smith and Conley[73] and by de Torregrosa, Ortiz, and Vargas.[146] Hemolytic anemia in the patient studied by the latter authors apparently resulted entirely from the structural defect associated with spherocytosis since the response to splenectomy was similar to that anticipated in patients with spherocytosis not associated with abnormal hemoglobin disease.

CONCLUSIONS

The outstanding known clinical and biochemical features of inherited errors in hemoglobin synthesis and the most widely accepted genetic aspects of these abnormal states have been presented. Solution of the many unanswered questions must await further application of analytical techniques now available, the development of more precise biochemical methods, further utilization of opportunities to survey large segments of the human population, and continued emphasis upon the necessity of studying relatives of affected individuals.

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VOL. 6 1957

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VOL. 6 1957

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Editorial

EPIDEMIOLOGIC ASPECTS OF CORONARY ARTERY DISEASE

Two useful discussions about the epidemiologic approach to the study of causes of coronary heart disease have been published very recently. The first is the Report of the World Health Organization Study Group on Atherosclerosis and Ischaemic Heart Disease.[5] The second,[2] by Dr. Herman Hilleboe, a member of that Study Group, covers some of the same ground but adds some data on national diets and mortality statistics supplied by Dr. Jacob Yerushalmy. These latter are offered as evidence that dietary fat is not the sole determining factor in the development of atherosclerosis or subsequent coronary heart disease.

This conclusion about the role of dietary fat is not novel and, in fact, no responsible investigator has ever proposed that dietary fat is the only factor involved. Many recent discussions, however, have concentrated on the question of dietary fat because as yet it appears to be the only factor, obviously capable of modification in efforts directed toward prevention, for which there is real evidence about its significance. And this evidence is by no means confined to epidemiologic data.

Dr. Hilleboe's conclusion about fats, or what he calls his "assumption," is that: "Human diets with unrestricted fats, especially some of the saturated fatty acids, appear to be associated with coronary atherosclerosis, particularly in adult males, but this is not a causal relationship." It appears that Dr. Hilleboe's extreme caution about drawing conclusions may be biased in favor of negative versus positive conclusions; surely the *lack* of causal relationship is no less difficult to prove than that a given effect is the result of a given cause. I doubt that Dr. Hilleboe really believes he has adequate evidence to state that there is *not* a causal relationship between dietary fat and the tendency to develop atherosclerosis in man.

But major criticism must be directed against the dietary and mortality data and their analysis cited in detail by Dr. Hilleboe. These data are used to make a comparison, for 12 countries, of dietary fat and the age-specific death rates ascribed to the sum of all heart diseases in the period 1950-1952. But, as will be seen, there are questions about these data, about their relevance to the question at hand, and about the temporal comparability of the data on the two variables. An examination of these questions will show how serious they are.

DO THE MORTALITY DATA PERTAIN TO CORONARY HEART DISEASE?

The data cited in Dr. Hilleboe's Table I, reproduced here, are for the total of all heart disease mortality as summed up in the 4 categories of the Abbreviated International List of Causes of Death: B-25 (Chronic Rheumatic Heart Disease), B-26 (Arteriosclerotic and Degenerative Heart Disease), B-28 (Hypertension With Heart Disease), and B-27 (Other Diseases of the Heart). It cannot be argued that an etiologic factor suggested to be involved in the development of

VOL
6
195

TABLE I. MORTALITY IN 12 COUNTRIES FROM HEART DISEASE FOR MALES AND PER CENT OF CALORIES DERIVED FROM FAT

COUNTRIES	RATES PER 100,000 BY AGE							PER CENT OF CALORIES FROM FAT
	40-44	45-49	50-54	55-59	60-64	65-69	70-74	
Australia	90.6	203.7	387.4	705.7	1161.9	1832.1	2750.9	33
Canada	121.8	238.6	424.2	711.2	1095.4	1555.6	2335.5	40
German Federal Republic	61.1	117.8	245.4	308.7	504.4	773.8	1307.6	35
Denmark	42.0	105.8	209.8	377.0	632.0	1011.6	1819.9	39
Israel	69.5	146.0	284.1	423.7	850.0	1125.4	1660.2	23
Italy	56.6	107.1	192.3	312.4	512.7	860.9	1518.2	21
Japan	46.7	73.6	113.9	190.2	303.8	512.2	713.1	8
Netherlands	36.8	72.5	156.4	253.7	454.4	780.8	1366.1	37
New Zealand	80.4	195.4	356.3	624.3	1084.4	1675.9	2536.7	40
Portugal	55.6	97.9	164.6	274.2	482.2	870.4	1432.1	25
Sweden	41.8	103.3	190.3	364.8	621.0	1050.8	1657.0	39
United States	159.1	308.1	542.6	883.9	1312.4	1931.2	2781.8	39

All countries for which the dietary source of calories are given in Working Paper No. 6 of the W.H.O. Study Group on Atherosclerosis and for which deaths from these diseases and recent population estimates are available were utilized. Deaths and population estimates are for the three-year period 1950-1952.

The cardiovascular diseases included in this group are those corresponding to the abbreviated list numbers B-25 to B-28.

These are: B-25—chronic rheumatic heart disease; B-26—arteriosclerotic and degenerative heart disease; B-27—other diseases of the heart; B-28—hypertension with heart disease.

Source of mortality and population data: WHO, Annual Epidemiological and Vital Statistics, 1950-1952; Working Paper No. 9, WHO Study Group on Atherosclerosis. (Reproduced by permission of Dr. H. E. Hilleboe.)

coronary heart disease must be equally involved in the production of *all* heart diseases. The total mortality from all heart diseases might provide a rough index as to the mortality from coronary heart disease only if it could be shown that coronary heart disease is a constant fraction of total heart mortality in the countries considered.

But this is clearly *not* the case. Category No. B-26, sometimes mistaken to mean simply coronary heart disease, does not represent the same proportion of the total heart mortality in the several countries. Category B-26 tends to be most nearly a constant proportion among middle-aged men but among men aged 50 to 54 years, dying in 1952, category B-26 accounted for 73 per cent in Denmark and Japan, 83 per cent in the United States, 87 per cent in New Zealand, and 92 per cent in Israel. This is bad enough but B-26 itself is a composite, corresponding to the sum of categories 420, 421, and 422 in the full International List of Causes of Death (Sixth Revision). For all countries category 420 is clearly used to indicate typical coronary heart disease with acute occlusion and myocardial infarction. Category 422 (myocardial degeneration) is accepted by many investigators as almost always pertaining to the same basic disorder of ischemic heart disease. But, what about Category 421?

Category 421 is described officially as "chronic endocarditis not specified as rheumatic, 'excluding' chronic endocarditis specified as syphilitic or gonococcal." It is really confined to disorders of the valves of the heart where the physician does not specify that he is sure of the origin. Customs in respect of specification about the origin of valvular disease differ greatly between different

countries. The physician in the United States seldom uses category 421 but puts his valvular cases in categories 410-416 (Chronic Rheumatic Heart Disease) whereas his colleagues in many other countries (e.g., Japan, Italy) are far less ready to specify that rheumatic fever was definitely the cause of the chronic valvular heart disease they observe in later life.

This is illustrated in Table II which compares Italy versus the United States white persons for the year 1951, that is in the center of the mortality period considered by Dr. Hilleboe. If category 421 means arteriosclerotic heart disease, most of the cardiac deaths of young women in Italy are caused by arteriosclerotic heart disease! We should be forced to the preposterous conclusion that death from arteriosclerotic heart disease is three times more common among young Italian women than among American white *men* of the same age.

TABLE II. DEATH RATES, PER 100,000, IN 1951. UNITED STATES WHITES AND ITALY

CAUSE OF DEATH	AGES 20-24				AGES 50-54			
	U.S.A.		ITALY		U.S.A.		ITALY	
	M	F	M	F	M	F	M	F
All causes	181	76	168	135	1,218	660	1,055	620
All heart (410-443)	7.8	6.0	10.0	12.9	544	183	189	126
401 (rheumatic fever with heart complications)	0.7	0.7	2.6	3.6	1.2	0.9	3.4	5.3
410-416 (chronic rheumatic heart disease)	3.8	3.3	0.9	1.2	27.0	25.8	5.0	6.9
420 (coronary)	1.9	1.0	0.5	0.1	423	92	62	12
421 (endocarditis, valvular)	0.2	0.2	4.7	5.4	5.9	3.6	28.0	31.7
422 (myocardial degeneration)	0.4	0.4	0.9	1.9	21.9	12.4	54.1	39.9
001-019 (tuberculosis)	5.2	12.5	40.6	54.8	46.5	11.1	110.4	30.6
Category XVII (violence)	124	22	57	11	124	35	89	19
All causes less tuberculosis and violence	52	42	70	69	1,048	614	856	570

Table II indicates that Italian doctors are reluctant to use the chronic rheumatic heart categories 410-416, preferring to specify "acute rheumatic fever with cardiac complications" (category 401) or valvular heart disease without further specification (category 421). The most reasonable interpretation of the data in Table II is that, compared with the United States, rheumatic fever is more common in Italy, that coronary heart disease in that country is far less frequent than in the United States, and that neither all heart disease mortality nor the mortality listed under B-26 is an acceptable basis for comparing coronary heart disease frequency in the two countries.

The data in Table I on the total death rate from all causes are of interest because they show that American males, in comparison with men in Italy of the same age, have a higher total mortality rate both in the twenties and in the fifties. The explanation for this excess differs for the younger and older men, however. Our young men too often die from violence while our older men are seemingly an easy prey to coronary heart disease. The mortality rate from this

disease is also excessive, apparently, among American women, especially, at older ages, compared with their Italian counterparts.

When the Japanese vital statistics are analyzed in similar detail, the attempt to include category 421 in arteriosclerotic or coronary heart disease produces even more startling absurdities. But the example in Table II, is enough, perhaps, to show the inadequacy of any analysis of coronary mortality based on the death rates from all heart disease or even on such combinations as category B-26 or the sum of categories 420, 421, and 422. We must conclude that the heart mortality data cited by Dr. Hilleboe are unacceptable indices of coronary heart disease.

ARE THE DIETARY AND MORTALITY DATA COINCIDENT?

If an attempt is to be made to inquire what, if any, relationship there is between the incidence of coronary heart disease and factors suspected of having a role in its causation, the data examined must embrace the two variables in the correct time sequence. In the case of coronary heart disease, perhaps 15 per cent of first attacks are fatal, but average survival after the disease is first clinically apparent is something of the order of 5 to 7 years. We might suggest, then, that mortality data in the period 1950-1952 refer in some cases to disease first appearing in that period but that the majority of the deaths in 1950-1952 were only the final outcome of disease clinically established some years earlier. Further in the search for the basic etiology, it is necessary to look for developments before the disease is clinically recognized. It is well known that the primary atherosclerosis usually develops long before the clinical appearance of the disease.

It is reasonable, then, to insist on consideration of dietary data prior to clinical illness if the question is about the possible influence of the diet on the development of atherosclerosis. For deaths in 1950-1952 the critical age period might be in the middle 40's. Of course, if the diet were substantially constant for many years preceding the death data, then dietary data from any of the intervening years would be representative.

But in Dr. Hilleboe's analysis, the dietary data are primarily for the year 1954, that is to say an average of 3 years *after* the recorded mortality data. In many of the countries considered by Dr. Hilleboe, the diet altered from 1950 to 1954, and there were very great changes in the previous decade. For example, the people in Finland, Norway, the Netherlands, and the German Federated Republic are known to have undergone years of severe fat restrictions in the 1940's.

In the data as tabulated by Dr. Hilleboe and Dr. Yerushalmy, the most striking departure from a good correlation between dietary fat in 1954 and heart mortality in 1950-1952 is the case of the Netherlands. But let us inquire about the diet when it might have been influential in that country. Table III summarizes the dietary data for 1936-1954. There are no reliable records for the war years, but it is known that food fats available in the Netherlands were greatly reduced from 1940-1944, that the diet was at the near starvation level, with extremely little fat, in 1944 and 1945, and the fat available in 1946 was less than in 1947.

Perhaps, if dietary fat is important in producing atherosclerosis, the mortality data for the Netherlands in 1960 will more properly reflect the 37 per cent

calorie level recorded for 1953-1955. But in no case is it proper to suggest that the deaths in 1950-1952 should reflect the diet of the surviving population in later years. A crude estimate of the Dutch diet during the decade prior to 1950-1952, when the diet should have been exerting such influence as it may have, might be around 20 to 25 per cent fat calories.

TABLE III. PERCENTAGE OF DIETARY CALORIES PROVIDED BY FATS IN THE NETHERLANDS*

YEAR	FAT CAL.	YEAR	FAT CAL. (PER CENT)
1936-1938	33.7 per cent	1948	28.8
1940-1944	Much Reduced (occupation)	1949	31.2
		1950	34.5
1944-1945	Very Low (famine)	1951	34.8
1946	Below 1947 value	1952	35.5
1947	27.3 per cent	1953	37.1
		1954	36.6
		1955	37.5

*See Voeding, Amsterdam, Jaarg. 16, No. 11, pp. 900-923, 1955; ibid Jaarg. 18, No. 3, pp. 180-183, 1957.

Similar considerations apply to Finland, Norway, to the German Federated Republic, and to a lesser extent, to Sweden and Switzerland. The prolonged influence of the war and its aftermath on the diets of many countries cannot be ignored. Even for Japan, where the diet in 1954 is so low in fats, the figures for the preceding decade are considerably lower. The situation among the Israelites probably bears similarities to that among the Norwegians but Israel presents additional complications.

DO THE DATA PERTAIN TO THE POPULATION AT RISK?

Israel, established only in 1946, is populated almost entirely by recent immigrants with a great diversity of dietary backgrounds whose diets, as well as those of the indigenous population, have changed much with the development of this country. The Jewish immigrants from Yemen, where they subsisted on a very low fat diet traditionally, have not yet caught up in coronary mortality with the Ashkenazim, some of whom arrived with recent backgrounds of privation but with earlier patterns of high fat diets. If indeed the diet is an important factor in the development of atherosclerosis it would be remarkable if the mean per capita food supply in Israel in 1954 should be in close conformity with the mortality in 1950-1952.

I have mentioned West Germany where the diet changed little during the war years but where the fat intake was very low for several years after the war. A further complication is the tremendous migration into this country since the war. A population of 40 million has taken in about 11 million refugees and escapees from the East. The immigrants, as is always the case, are not a good sample in regard to age, vigor, and state of health of the population from which they migrated. And in the case of West Germany the majority of the immigrants left behind them a diet very different from that of their new land of settlement.

Australia bears some resemblance to West Germany in this respect. In 1952, the end year of Dr. Hilleboe's mortality data, the population of Australia was 8,700,000. In the six years preceding, the permanent migration arrivals in Australia from overseas totaled 416,000 persons whose dietary backgrounds and predilections were by no means identical with those of the indigenous Australians. As in the cases of Israel and West Germany, the per capita fat supply in 1954 gives a distorted picture of the diet of the actual population at risk.

THE NATIONAL DIETARY DATA

The Nutrition Division of the Food and Agriculture Organization supplied at short notice the dietary data cited by Dr. Hilleboe and is presently engaged in an effort to improve these tentative estimates derived from information on agricultural production and food shipments. This information is mainly in terms of foods, not nutrients, and even the food data are far from being of uniform reliability. The translation of these bulk data into average nutrients consumed by the adult population, which is the only item of relevance, raises many questions. F.A.O., which supplied the data used by Dr. Hilleboe, made no attempt to estimate nutrients per adult.

OL.
6
957

In any case, it is difficult to understand how some of the percentage fat calorie figures were derived. For example, an independent analysis of the Australian food data yields an average of 38 per cent fat calories instead of the 33 per cent cited. For Canada and the United States the governments concerned have provided their own analyses of their own data and the results do not conform to the figures given in Dr. Hilleboe's Table I which indicate that Canadians have a diet higher in fat than do Americans. The United States data are given by the United States Department of Agriculture.* The figures for Canada are available beginning in 1935.† For every year of comparison, the official figures place the fat calories percentage of the United States above that of Canada, not below. For the United States the average for the 10 years ending in 1952 was 39.1 compared with 35.9 per cent calories from fats for Canada. The latest figures for the United States are from the 1955 Household Surveys: Urban, 44.9; Rural Nonfarm, 42.5; Farm, 41.8 per cent calories from fats.

At best, national average diets do not provide the crucial information desired unless the composition of the diet with regard to fat is constant for both sexes and at all ages. In all countries children tend to consume a disproportionate amount of the total dairy products, but the share of milk and ice cream used by adults varies greatly from country to country. With regard to coronary heart disease the population at risk is the adult population, of course, though the beginnings of atherosclerosis may extend back to youth. Obviously, then, a more critical analysis of the relationship of the diet to the development of coronary heart disease calls for dietary data broken down by age and sex.

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*Misc. Publ. No. 691 and Supplement for 1949 and the U.S.D.A. Household Food consumption surveys, e.g., 1955, Reports 1-6.

†Canadian Bulletin on Nutrition, Department of Public Printing and Stationery, Ottawa, Vol. 3, 1953, and subsequent issues.

Equally important may be more detailed information about the kinds of fats consumed. Dr. Hilleboe alludes to the difference between types of fats. There is no doubt that the more saturated fats have more influence on the blood cholesterol concentration than do the majority of the natural food oils.[1,4] Though there is no proof that there is a corresponding difference in influence on the development of coronary heart disease, the indirect evidence is strong that the greatest concern should be felt about the common meat and dairy fats that now occupy so large a place in the American diet. National dietary data broken down in this way are scanty as yet but in the meantime the best indirect indication as to the amount of such animal fats in the diet are data on animal protein consumption. Information on the animal protein in the diet has been tabulated for many years; nutritionists were long interested in this nutrient for reasons quite different from our present concern. And it is significant that heart disease mortality in populations tends to be related to animal protein consumption much as it is to total fat consumption.

Dr. Hilleboe infers from the latter fact that protein may be as much implicated in atherogenesis as is fat. But it should be observed that the only experimental evidence for an effect of protein is from experiments where protein deficiency, not abundance, in the diet tended to promote atherosclerosis in some animals. Controlled experiments on man fail to reveal any influence on the blood cholesterol system of variations in intake of animal protein covering the range of all ordinary diets.[3] Such epidemiologic suggestions as there are for an effect of animal protein are readily accounted for by the high correlation between animal protein and animal fat intakes in most human populations.

LIMITATIONS AND OPPORTUNITIES FOR EPIDEMIOLOGY

Epidemiologic investigations promise to make major contributions to the discovery and application of effective control and preventative measures against coronary heart disease. Though even properly conducted epidemiologic studies have limitations, they offer several kinds of utility. It is foolish to ask epidemiology for basic information on the mechanism whereby an environmental factor produces or influences the development of a disease, but it can provide clues for research by other methods, and it provides a device for testing hypotheses, not as to truth or falsity, but merely as to consistency with the distribution of the disease in question.

When the frequency of a disease and some environmental factor tend to vary in the same direction, this is a clue to be followed up by similar epidemiologic methods applied in a wider variety of circumstances and by such experiments as may be feasible. On the other hand, a hypothesis about a relationship between any two or more variables that may be represented in populations, including a disease or a factor known to have some basic relationship to it, may be tested by comparisons within and between populations. This is not a test to prove causality which is seldom accessible to critical test by epidemiology but simply a way to decide whether the hypothesis is consistent with the distribution of the disease.

The major contributions of epidemiology in the past have been made in areas where the time sequence of cause and effect is short and where epidemiologists have been expert in the scientific knowledge of the disease in question or of the associated variables or both. The present situation in regard to coronary heart disease is somewhat different. The time sequence between the start of the operation of environmental factors and clinical recognition of the disease seems to be measured in years, perhaps many years, instead of weeks. Moreover, few epidemiologists have, as yet, devoted themselves to the field of cardiovascular diseases with the intensity and technical understanding of the variables at issue characteristic of the more familiar infectious diseases. This is a new area for epidemiologic inquiry and many of the variables will require specialized physiological and biochemical attention.

In any case it is essential to insist that the numerical data be accurate, that the variables selected for epidemiologic analysis be precisely defined, that the numerical representation offered is actually that of the purported variable, and that the time sequence appropriate to the disease be preserved. Finally, if the inquiry is primarily an epidemiologic one, legitimate conclusions will be restricted to: (1) advice as to which variables may merit further study, and (2) decision as to whether or not the epidemiologic data are consistent with the hypothesis in question. This does not mean that a one-to-one relationship can be demanded unless the hypothesis under scrutiny proposes to identify one single variable as the sole and exclusive cause and influence for all cases of the disease. With all other hypotheses some degree of correlation is all that can be asked to establish consistency.

It is evident that real understanding will come not from epidemiology alone, but from the use of all of the disciplines of medical research. In such a universal attack on the problems of coronary heart disease and its prevention, epidemiology will be a powerful tool.

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ANCEL KEYS, PH. D.
LABORATORY OF PHYSIOLOGICAL HYGIENE
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA
MINNEAPOLIS 14, MINN.